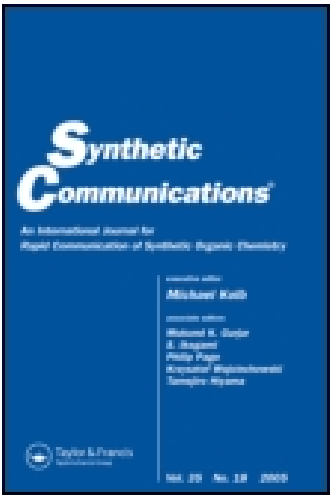

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THE PAUSON-KHAND REACTION IN SYNTHESIS OF BICYCLIC RIGID α-AMINO ACIDS

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THE PAUSON-KHAND REACTION IN SYNTHESIS OF BICYCLIC RIGID α-AMINO ACIDS

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ABSTRACT

The combination of intramolecular Pauson-Khand methodology for $Co_2(CO)_8$ mediated cyclization, and the Schöllkopf chiral auxiliary for stereoselective preparation of appropriate 1,6-heptenynes constitutes a powerful method for the preparation of rigidified bicyclic α-amino acids.

INTRODUCTION

α-Substituted α-amino acids are conformationally constrained and will constitute a powerful approach for generating structurally defined peptides as conformational probes and bioactive agents when incorporated into peptides.[1–5] Such findings have stimulated a search for ways to prepare conformationally constrained amino acids. Our efforts have largely been directed toward the development of stereoselective methodology for the preparation of rigid cyclic amino acids where the α-carbon of the amino acid is imbedded in the ring.[6–10] The chiral information required for the

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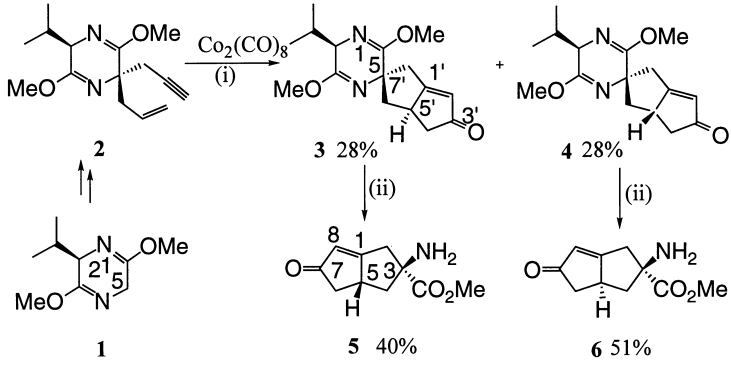
preparation of these structures is available in the Schöllkopf bislactim auxiliary **1** as a substrate for stereoselective alkenylation and alkynylation. The bislactim ether **1** is derived from an enantiomerically pure diketopiperazine of valine and glycine.[11] Subsequent cyclization reactions by Pd(0)-catalysis or Ru(II)-RCM reactions have been found compatible with the bislactim moiety and have been highly useful for the construction of rigid cyclic α-amino acids.[6–10] In this report we show that cobalt complexes under the Pauson-Khand conditions are also compatible with the bislactim moiety and can become highly useful for the construction of bicyclic α-amino acids. The cyclopentenone ring moiety in the pentalene system **3** and **4** is inherently functionalized for further chemical transformations if desired. In the family of pentalenes, a recent report describes related structures in the form of a racemic synthesis of 3-aminobicyclo[3,3,0]octane-1,3-dicarboxylic acids as conformationally constrained glutamic acid. The products were enatiomerically resolved as diastereomeric salts.[12]

RESULTS AND DISCUSSION

In the preparation of the substrate **2** for the Pauson-Khand transformation, the stereoselectivity in the first alkylation step of the auxiliary **1**, which generates a new stereogenic center at C-5, is of little significance because the stereochemistry is lost when the first product is remetalated with *n*BuLi. In general, the second alkylation has been found to be highly stereoselective with the new substituent entering *trans* with respect to the isopropyl group.[6–9] In substrate **2**, the stereochemistry at C-5 has been formed by an initial allylation, which is followed by alkynylation. The stereochemistry at C-5 is conveniently changed by altering the order of the alkylation reactions. In this manner the other enantiomers of the amino acids **5** and **6** would be available without having to change the chiral auxiliary **1** to its enantiomeric structure (Scheme 1).

The Pauson-Khand reaction, a formal [2+2+1]cyclization, in its intramolecular form is a powerful method for the construction of bicyclic annulated cyclopentenone derivatives.[13,14] In the present case, the intramolecular Pauson-Khand reaction with the 4,4-disubstituted 1,6-enyneheptane **2** was to be effected under conditions with stoichiometric amounts of dicobaltoctacarbonyl in the presence of an *N*-oxide to promote the reaction at low temperature to avoid decomposition of the bislactim moiety.[15] As intended, the enyne complex with dicobalthexacarbonyl was formed from the substrate **2** and dicobaltoctacarbonyl in hexane at ambient temperature. Evaporation of the solvent and redissolution of the complex in dichloromethane and subsequent addition of an excess of



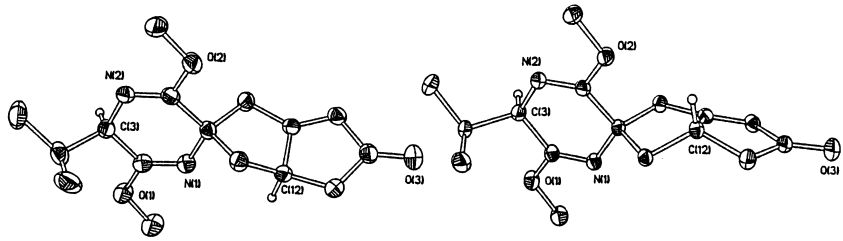
Scheme 1. (i) a: hexane, 20°C, 1 h, b: $MeN(O)(CH_2CH_2)_2O{\cdot}H_2O$, CH_2Cl_2, 20°C, 0.5 H; (ii) 0.25 M HCl, dioxane, 20°C, 5 h.

N-methylmorpholine *N*-oxide furnished the spiroannulated Pauson-Khand products **3** and **4**.The stereogenic centers in the bislactim ring did not exert any significant diastereoselective control on the cyclopentenone annulation reaction. The overall yield was 56% of the pentalene spiranes **3** and **4** as a 1:1 mixture. A similar finding has been reported for a simpler related structure, *viz*. a 4,4-disubstituted 1,6-heptenyne by a methyl and an ethoxycarbonyl group.[16] In this case it was proposed that the almost complete lack of stereoselectivity was caused by low steric differentiation between the 4,4-geminal substituents. Substituents on the allylic or propargylic carbons, however, may influence the sterical course. Thus it has been found that high stereoselectivity may be achieved in 3,4- and 4,5-disubstituted 1,6-heptenynes, and that the selectivity is influenced by the nature and relative stereochemistry of the substituents.[17,18]

The stereoisomers **3** and **4** were readily separated by flash chromatography and were obtained in crystalline state. Their structures and relative stereochemistry at C-5′ in the bicyclo[3,3,0]octane moiety have been established by single crystal x-ray analysis, as given in formulae **3** and **4**. The ORTEP diagrams of the x-ray structures are presented in Fig. 1.

Both isomers **3** and **4** were hydrolyzed separately under mild acid conditions to the target amino acids **5** and **6**. The latter, as well as the Pauson-Khand spiranes **3** and **4**, can also be regarded as functionalized building blocks suitable for further chemical transformations.

In conclusion, we have shown that the Pauson-Khand reaction is compatible with the bislactim ether auxiliary (2*R*)-2,5-dihydro-3,6-dimethoxy-2-isopropyl-5-pyrazine and can be used in stereoselective constructions of bicyclic α-amino acid where the ring carbon of the amino acid is imbedded in the pentalene ring system.



Compound **3** Compound **4**

Figure 1. The ORTEP plot of the x-ray structure of compounds **3** and **4**. Ellipsoids are shown at 50% probability. For clarity only hydrogens at stereogenic centers are shown. The absolute configurations at the stereogenic centers were established relative to the known chirality (2*R*) at (C3) (**1**).

EXPERIMENTAL

^{1}H NMR spectra were recorded in $CDCl_3$ at 300 MHz or 500 MHz using a Bruker DPX 300 or DPX 500. ^{13}C NMR spectra were recorded in $CDCl_3$ at 75 MHz or 125 MHz using the above instruments. Chemical shifts are reported in ppm using residual $CHCl_3$ (7.24 ppm) and $CDCl_3$ (77 ppm) as references. *J* values are given in Hz. Mass spectra were recorded under electron impact conditions at 70 eV (EI) using a VG Prospect instrument. The spectra are presented as *m*/*z* (% rel. int.). IR spectra were recorded on a Perkin-Elmer 1310 infrared spectrophotometer or a Nicolet Magna FT-IR 550 spectrometer with Attenuated Total Reflectance (ATR spectra). Hexane and dichloromethane were dried over a molecular sieve. Silica gel for flash chromatography was Merck Kiselgel 60 (F254).

(2*R*,5*S*,5′*R*)-2,5-Dihydro-3,6-dimethoxy-2-isopropylpyrazine-5-spiro(3′-oxobicyclo[3,3,0]oct-1′-en-7′-yl) (3) and (2*R*,5*S*,5′*S*)-2,5-Dihydro-3,6-dimethoxy-2-isopropylpyrazine-5-spiro (3′-oxobicyclo[3,3,0]oct-1′-en-7′-yl) (4)

A solution of (2*R*,5*S*)-5-allyl-2,5-dihydro-3,6-dimethoxy-2-isopropyl-5-(2-propynyl)pyrazine (**2**)[8] (578 mg, 2.21 mmol) in dry hexane (5 mL) was added dropwise with stirring to a suspension of octacarbonyldicobalt (840 mg, 2.21 mmol, 90–95%) in dry hexane (15 mL) under argon at ambient temperature. The reaction mixture was evaporated to dryness at reduced

pressure after stirring for 1 h. Dichloromethane (15 mL) added to the residual material followed by solid *N*-methylmorpholine *N*-oxide monohydrate (1.79 g, 13.26 mmol). The mixture was stirred at ambient temperature for 0.5 h before the reaction was quenched by addition of 1 M phosphate buffer (pH 7, 15 mL). The aqueous phase was extracted with diethyl ether (3×20 mL), the combined organic solution dried ($MgSO_4$), evaporated at reduced pressure, and the residual material subjected to flash chromatography using Et_2O:hexane 1:1. The isomeric products **3** and **4** were obtained as white solids in yields 179 mg (28%) and 181 mg (28%), respectively.

Compound 3

M.p. 58–59°C. (Found: C, 66.10; H, 7.85. $C_{16}H_{22}N_2O_3$ requires C, 66.19; H, 7.64%). HRMS: M 290.1630. $C_{16}H_{22}N_2O_3$ requires 290.1630; ν_{max}(ATR)/cm^{-1} 2964, 1713, 1690, 1634, 1237; δ_H(500 MHz) 0.65 (3 H, d, *J* 6.8, CH_3), 1.02 (3 H, d, *J* 6.8, CH_3), 1.78–1.90 (2 H, m, CH_2), 2.08 (1 H, dd, *J* 17.8, 3.6, C*H*H), 2.21 (ds, *J* 3.2, 6.8, 1 H, $(CH_3)_2CH$), 2.57–2.62 (m, 2 H, 2×C*H*H), 3.11–3.15 (1 H, m, CHH), 3.52–3.57 (1 H, m, CH), 3.59 (3 H, s, OCH_3), 3.62 (3 H, s, OCH_3,), 3.96 (1 H, d, *J* 4, 0 H-2), 5.87 (1 H, t, *J* 1.1, CH=); δ_C (125 MHz) 16.8 (CH_3), 19.2 (CH_3), 31.1 (Me_2CH-), 42.1 (CH_2), 43.1 (CH_2), 44.7 (CH), 45.9 (CH_2), 52.2 (OCH_3), 52.5 (OCH_3), 60.85 (C-2), 65.4 (C-5), 124.7 (CH=), 161.3 (C), 163.65 (C), 188.24 (C=), 210.4 (CO); *m*/*z* 290 (M^+, 63), 259 (58), 247 (100), 219 (18), 217 (30), 195 (50), 196 (61), 154 (94).

Compound 4

M.p. 82–83°C. (Found: C, 65.84; H 7.73. $C_{16}H_{22}N_2O_3$ requires C, 66.19; H, 7.64%). HRMS: M 290.1629. $C_{16}H_{22}N_2O_3$ requires 290.1630; ν_{max}(ATR)/cm^{-1} 2960, 1712, 1690, 1635, 1234; δ_H (500 MHz) 0.63 (3 H, d, *J* 6.8, CH_3), 1.03 (3 H, d, *J* 6.8, CH_3), 1.46 (1 H, t, *J* 12.3, C*H*H), 2.08 (1 H, dd, *J* 17.8, 3.3, C*H*H), 2.18 (1H, ds, *J* 6.8, 3.2, (Me_2CH), 2.23 (1 H, *J* 12.7, 8.6, C*H*H), 2.56–2.61 (2 H, m, 2×C*H*H), 3.19 (1 H, d, *J* 12.7, C*H*H), 3.39–3.45 (1 H, m, CH), 3.57 (3 H, s, OCH_3), 3.68 (3 H, s, OCH_3), 3.95 (1 H, d, *J* 4,0, H-2), 5.89 (1 H, s, CH=); δ_C (125 MHz) 16.8 (CH_3), 19.3 (CH_3), 31.0 (Me_2CH-), 42.8 (CH_2), 43.4 (CH_2), 45.9 (CH), 47.3 (CH_2), 52.35 (OCH_3), 52.6 (OCH_3), 61.0 (C-2), 64.7 (C-5), 125.1 (CH=), 162.0 (C), 165.0 (C), 188.3 (*C*=), 210.5 (CO); *m*/*z* 290 (M^+, 49), 259 (68), 247 (88), 219 (17), 217 (33), 195 (64), 196 (85), 154 (100).

Methyl (3*S*,5*R*)-3-amino-7-oxobicyclo[3,3,0]oct-8(1)-ene-3-carboxylate (5)

1 M HCl (8 mL) was added to a solution of (2*R*,5*S*,5′*R*)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine-5-spiro(3′-oxobicyclo[3,3,0]oct-1′-en-7′-yl) (**3**) (566 mg, 1.95 mmol) in dioxane (16 mL) and water (8 mL) at ambient temperature. The mixture was stirred for 5 h, pH adjusted to 10 by addition of conc. aq. ammonia, and the mixture extracted with dichloromethane (3×20 mL). The combined organic phases were dried ($MgSO_4$), the solvent distilled off at reduced pressure, and the residual material subjected to flash chromatography using 3% methanol in dichloromethane; yield 195 mg (51%) as a colorless oil. HRMS: M 195.0890. $C_{10}H_{13}NO_3$ requies 195.0895; ν_{max}(film)/cm^{-1} 3369(b), 2955, 1704, 1633, 1299, 1036; δ_H (300 MHz) 1.61 (1 H, app.t, *J* 12.3, C*H*H), 1.77 (2 H, br.s, NH_2), 1.87–2.12 (2 H, m, 2×C*H*H), 2.32–2.60 (2 H, m, 2×C*H*H), 3.11 (1 H, d, *J* 18.0, C*H*H), 3.40–3.43 (1 H, m, CH), 3.65 (3 H, s, OCH_3), 5.82 (1 H, s, CH=); δ_C (75 MHz) 40.5 (CH_2), 41.9 (CH_2), 43.8 (CH_2), 44.5 (CH), 52.5 (OCH_3), 65.7 (C-3), 125.4 (CH=), 176.6 (CO), 187.21 (C=), 209.7 (CO); *m*/*z* 195 (M^+, 20), 178 (5), 136 (100), 119 (6), 108 (13), 102 (54), 94 (31), 91 (9).

Methyl (3*S*,5*S*)-3-amino-7-oxobicyclo[3,3,0]oct-8(1)-ene-3-carboxylate (6)

Was prepared as above from (2*R*,5*S*,5′*S*)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine-5-spiro(3′-oxobicyclo[3,3,0]oct-1′-en-7′-yl) (**4**) (785 mg, 2.71 mmol) and was isolated as an oily material after flash chromatography; yield 211 mg (40%). HRMS: Found: M 195.0886. $C_{10}H_{13}NO_3$:requires 195.0895; ν_{max}(film)/cm^{-1} 3371(b), 2955, 1703, 1630, 1260, 1043 cm^{-1}; δ_H (300 MHz) 1.17 (1 H, app.t. *J* 12.3, C*H*H), 1.79 (2 H, br.s, NH_2), 1.94 (1 H, dd, *J* 12.0, 3.1, C*H*H), 2.34–2.63 (3 H, m, 3×C*H*H), 3.06–3.16 (2 H, m, CH and C*H*H), 3.61 (3 H, s, OCH_3), 5.75 (1 H, br.s, CH=); δ_C (75 MHz) 41.4 (CH_2), 42.2 (CH_2), 44.6 (CH_2), 45.0 (CH), 52.4 (OCH_3), 65.3 (C-3), 125.2 (CH=), 176.6 (CO), 186.2 (C=), 209.4 (CO); *m*/*z* 195 (M^+, 10%), 178 (4), 136 (100), 119 (3), 108 (23), 102 (51), 94 (39), 91 (15).

X-Ray Crystallographic Analysis Data for Compounds 3 and 4

The crystal structures have been deposited at the Cambridge Crystallographic Data Centre and allocated the deposition numbers CCDC 145874/CCDC 145875.

Data for Compound 3

$C_{16}H_{22}N_2O_3$ (290.36); orthorhombic; space group $P2_12_12_1$: a=8.642 (1), b=12.110(1), c=14.897(1) Å; V=1559.05(6) Å^3, Z=4; D_c=1.237 Mg/m^3; F(000)=624. Data were collected on a Siemens SMART CCD diffractometer[19] using graphite monochromated MoKα radiation (λ=0.71073 Å, μ=0.086 mm^{-1}). Data collection method: ω-scan, range 0.6°, crystal to detector distance 5 cm, temperature 150(2) K. 21630 reflections were measured, of which 4736 were independent reflections with 2θ in the range of 5.4°–61.2°, R_{int}=0.058. The structure was determined and refined using the SHELXTL program package.[20] The non-hydrogen atoms were refined anisotropically, hydrogen positions were calculated from geometrical criteria and refined with isotropic thermal parameters. 278 parameter refined against 4736 F^2. Final R indices were R1=0.054 for $I_o > 2\sigma(I_o)$ and 0.065 for all data (residual $\delta\rho$ < 0.43 e.Å^{-3}).

Data for Compound 4

$C_{16}H_{22}N_2O_3$ (290.36); orthorhombic; space group $P2_12_12_1$: $a = 8.894(1)$, $b = 11.369(1)$, $c = 15.058(1)$ Å; $V = 1522.44(6)$ Å^3, $Z = 4$; $D_c = 1.267$ Mg/m^3; $F(000) = 624$. Data collection as above. 24452 reflections were measured, of which 5781 were independent reflections with 2θ in the range of 5.3°–66.3°, R_{int}=0.062. The structure was determined and refined using the SHELXTL program package.[13] The nonhydrogen atoms were refined anisotropically, hydrogen positions were calculated from geometrical criteria and refined with isotropic thermal parameters. 278 parameter refined against 5781 F^2. Final R indices were R1=0.042 for $I_o > 2\rho(I_o)$ and 0.053 for all data (residual $\delta\rho < 0.35$ e.Å^{-3}).

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