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Dihydrobenzopyran skeleton from β-lactams: a stereoselective ring opening–ring closure reaction sequence

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Abstract—Sodium borohydride treatment of the enantiomerically pure tricarbonyl(η^6-arene) chromium(0) complexed β-lactam **7** promoted a stereoselective ring opening–ring closure reaction sequence leading to the novel dihydrobenzopyran derivative **9** in good yield.

1. Introduction

Recently a number of efforts in the β-lactam antibiotics area have been made to synthesise novel classes of antibacterial agents[1] featuring a broad activity spectrum and a better resistance to β-lactamases.[2] In this context, tricyclic β-lactams are promising substrates, for example, the Sanfetrinem **1** developed and commercialised by Glaxo-Wellcome (Fig. 1).[3]

We have recently reported the synthesis of several new tricyclic β-lactams; namely racemic benzopirano[2,3-*c*]-azetidin-2-one **2**[4] and enantiopure benzofuro[3,4-*b*]-azetidin-2-one **3**[5] and azetidino[4,1-*d*][1,4]benzoxazepine **4** (Fig. 1).[6] In particular, the synthetic approach to **3** started from the enantiomerically pure tricarbonylchromium complexed benzilideneamine, which was in turn transformed to the tricarbonyl-[*N*-(4-methoxyphenyl)-3-hydroxy-4-(2-fluorophenyl)azetidin-2-one]chromium **6**. The latter, thanks to the high stereocontrol provided by the chromium-complexed arene moiety, was obtained as a single and enantiopure stereoisomer. The subsequent intramolecular nucleophilic aromatic substitution of the 3-hydroxy-substituted **6** gave **3**[5] (Scheme 1).

To extend the above procedure to the tricyclic 2,3-dihydroindole derivatives **11**, the enantiopure tricarbonyl[*N*-(4-methoxyphenyl)-3-amino-4-(2-fluorophenyl)-azetidin-2-one]chromium **10** was needed (Scheme 2). Recently, we have reported[7] the synthesis of enantiomerically pure 3-amino-2-azetidinones by using the $Cr(CO)_3$ complexed arene moiety as a chiral auxiliary. Our interest was concerned with the level of stereocontrol exerted by that chiral auxiliary on the two newly-formed stereocentres of the β-lactam ring through the Staudinger cycloaddition. Then, the

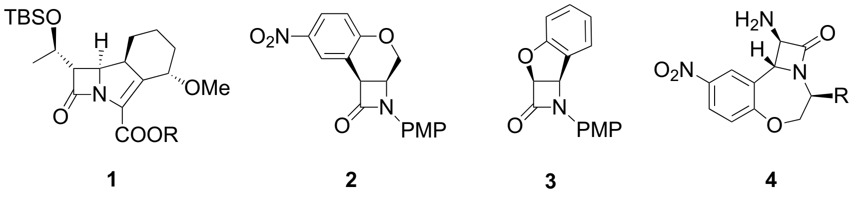

Figure 1.

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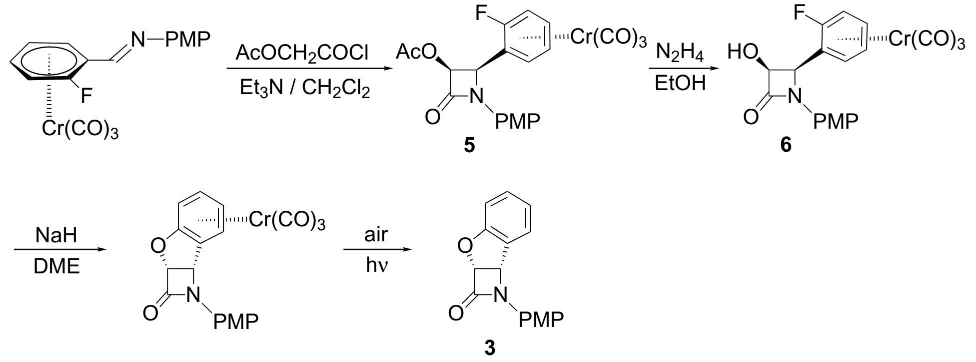
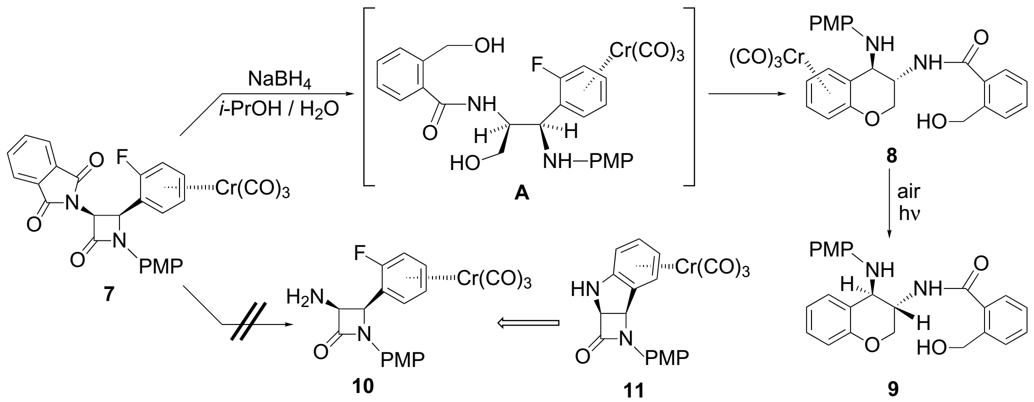


Scheme 1.



Scheme 2.

$Cr(CO)_3$ group was removed before restoring the amino function by cleavage of the phthalimido protecting group.

Herein we are interested in exploring the synthetic capabilities of the chromium complexed 3-amino-2-azetidinone **10** towards nucleophilic attack and as a useful precursor for the tricyclic system **11**.

2. Results and discussion

The [2 + 2] cycloaddition from the racemic tricarbonyl[*N*-(2-fluorobenzylidene)-4-methoxyaniline]chromium and phthalimidoacetyl chloride in dichloromethane and in the presence of triethylamine afforded the *cis*-β-lactam **7** as a single diastereoisomer (94%). Following the known procedure for the removal of the phthalimido group already used by us[7] in the case of the uncomplexed analogues, we have treated the tricarbonylchromium complexed phthalimido β-lactam **7** with hydrazine in methanol. However, the expected complexed 3-amino β-lactam **10** was not obtained, the only recovered products being unreacted **7** (60% yield).

After this negative trial, we looked for another way in order to remove the phthalimido pendant. It is known that treatment of uncomplexed 3-phthalimido β-lactams with sodium borohydride in aqueous/methanolic solution followed by acidic hydrolysis give rise to the corresponding 3-amino derivative.[8] By treating **7** under these conditions, we were surprised to recover a new compound in 65% yield to which was assigned the formula **8** on the basis of spectroscopic and analytical data (Scheme 2).

Compound **8** could arise from the expected reduction of the phthalimido pendant which was paralleled by the unusual reductive ring opening of the β-lactam. To this point, the basic medium may promote the nucleophilic intramolecular aromatic substitution of bis-carbinol intermediate **A** through a 6-*exo*-trig ring closure. It may be added that the fluorine atom on the complexed arene ring is activated towards nucleophilic aromatic substitution. The latter is possible only after rotation around the C_3–C_4 bond of the azetidinone ring; the value of the coupling constants of the two hydrogens on C_3 and C_4 of the benzopyran ring are only consistent with a *trans* arrangement.

The reductive cleavage of the β-lactam ring under the above conditions is surprising in the light of literature data,[9,10] which claims that more vigorous reagents ($LiAlH_4$ or borane) are needed in order to achieve such a transformation. Furthermore, it is known that the reduction of formyl or carbonyl groups at the side chain

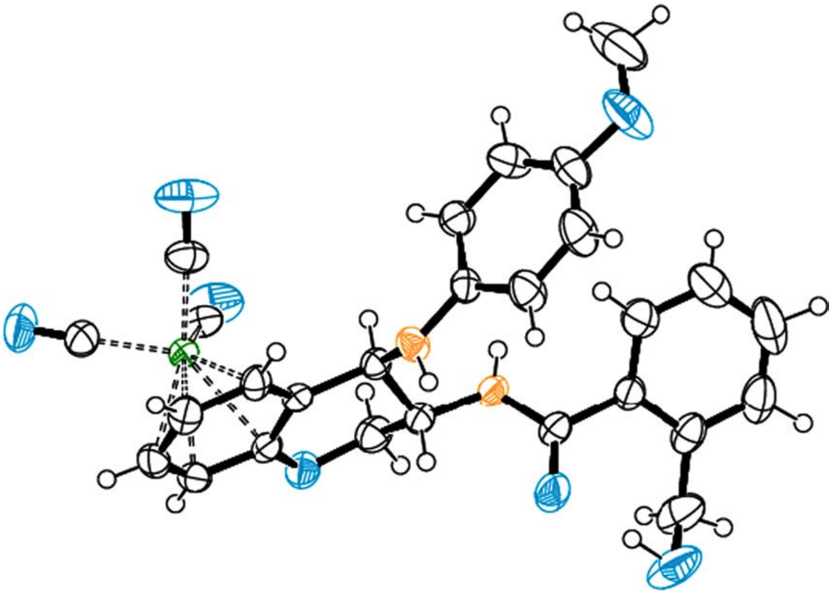


Figure 2. ORTEP plot of compound **8**. Atomic displacement parameters at 50% probability level; H atoms not to scale. Colour code: green = Cr, orange = N, blue = O, black = C,H.

of a β-lactam takes place without affecting the azetidinone ring.[11]

We then repeated the reaction under the same conditions on the uncomplexed 3-phthalimido-4-(2-fluorophenyl)-azetidin-2-one. The expected 2-hydroxymethyl benzamide was recovered as the only product in quantitative yield.

To this point, the reaction sequence was performed on the enantiomerically pure β-lactam **7** and the enantiomeric excess was determined by ^{1}H NMR with Eu(hfc)$_3$ as chiral shift reagent on the decomplexed sample **9** (ee ⩾98%).

A single crystal of enantiopure **8** was submitted to X-ray analysis[12] to confirm the proposed (3*S*,4*S*) structure (Fig. 2). The absolute configuration of decomplexed **9** is therefore (3*S*,4*R*) starting from (+)-(1*S*)-tricarbonyl[*N*-(2-fluorobenzylidene)-4-methoxyaniline]chromium, and that of the two stereocentres of the β-lactam **7** is also assigned thus following the accepted model for the diastereoselection in the chiral Cr(CO)$_3$ complexed arenes[13] (see Fig. 2).

3. Summary

In conclusion, β-lactams obtained in good yield and in enantiopure form using as starting material enantiomerically pure Cr(CO)$_3$ complexed imine can be converted in dihydrobenzopyran derivatives. The generality of this unexpectedly easy reductive ring opening may constitute a new approach to the synthesis of novel, highly functionalised dihydrobenzopyranes. In addition, the possibility to recover the enantiopure β-amino alcohol intermediate may open the way to their use as chiral ligand in the catalytic reactions.

4. Experimental section

The reactions were performed under nitrogen atmosphere. Column chromatography and TLC were carried out using, respectively, silica gel 60 and silica gel 60 F$_{254}$ pre-coated plates. The melting points were measured using a Büchi 510 apparatus and are uncorrected. The IR spectra were recorded using a 1725X FTIR spectrometer. NMR spectra were recorded in CDCl$_3$ using AMX 300 spectrometer. Evaluation of enantiomeric excess was performed using Eu(hfc)$_3$ (tris-[3-(heptafluoropropyl-hydroxymethylene)-(+)-camphorato]europium(III) as the chiral shift reagent. The optical rotations were measured using a Perkin–Elmer 241 Polarimeter with 1 dm pathlength at 25 °C.

4.1. Tricarbonyl-[3(*S*)-(2-hydroxymethyl)benzamido-4(*S*)-(4-methoxyphenyl)amino-benzopyrane]chromium 8

To a suspension of **7** (0.15 g, 0.29 mmol) in *iso*-propanol (6 mL) and water (0.8 mL), NaBH$_4$ (54 mg, 1.41 mmol) was added at room temperature. The reaction mixture was stirred for 20 h and monitored by TLC (silica gel, eluent ethylether/light petroleum 9/1). During this time the suspension became clear. The reaction was quenched with a saturated solution of brine (20 mL) and extracted with ethyl acetate (3 × 30 mL). The combined organic layer was dried over sodium sulfate and evaporated under reduced pressure giving **8** (0.10 g, 65%) as yellow solid, mp 106 °C (from light petroleum). $[\alpha]_D^{25} = +161.8$ (*c* 0.092, CHCl$_3$). ν_{max} (Nujol) 3340, 1960, 1870, 1640 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 3.80 (s, 3H), 3.85 (m, 2H exchangeable), 4.30 (dd, 2H, *J* 11.6, 4.2), 4.40 (ddd, 2H, *J* 11.6, 7.5, 2.0), 4.5–4.6 (AB system 2H), 4.70 (m, 1H), 5.00 (t, 1H, *J* 6.2), 5.30 (d, 1H, *J* 6.9), 5.50 (t, 1H, *J* 6.9), 5.60 (d, 1H, *J* 6.2), 6.8–7.6 (m, 8H); ^{13}C NMR (CDCl$_3$) δ 47.16, 53.07, 56.19, 65.16, 66.42, 81.29, 87.93, 92.65, 94.12, 94.46, 115.12, 115.72, 128.53, 128.65, 131.23, 132.18, 134.69, 138.18, 140.05, 140.66, 153.76, 170.57, 232.82; MS *m*/*z* 540 (M$^+$). Anal. Calcd for $C_{27}H_{24}CrN_2O_7$: C, 60.00; H, 4.47; N, 5.18. Found: C, 60.11; H, 4.49; N, 5.20.

4.2. 3(*S*)-(2-Hydroxymethyl)benzamido-4(*R*)-(4-methoxyphenyl)amino-benzopyrane 9

A solution of **8** (80 mg, 0.2 mmol) in dichloromethane (6 mL) was exposed to air and sunlight for about 6 h (the reaction progress was followed by TLC). The solvent was removed under reduced pressure, the residue was taken up with diethylether and filtered over a pad of Celite to remove the chromium salts. The ethereal solution was evaporated and the residue was crystallised by light petroleum affording **9** (60 mg, 98%) as white solid, mp 169 °C (from light petroleum). $[\alpha]_D^{25} = -156.1$ (*c*, 0.13 $CHCl_3$). Ee >95%. ν_{max} (Nujol) 3370, 1640 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.6 (m, 1H), 3.70 (m, 1H), 3.80 (s, 3H), 3.85 (t, 1H, *J* 6.3), 4.30 (dt, 1H, *J* 11.5, 4.6, 2.5), 4.55 (dd, 1H, *J* 11.5, 1.6), 4.5–4.6 (AB system, 2H), 4.53 (m, 1H), 4.67 (dq, 1H, *J* 7.8, 4.2, 2.5), 7.0–7.5 (m, 12H); ^{13}C NMR ($CDCl_3$) δ 47.14, 52.45, 56.25, 64.61, 65.05, 112.57, 114.55, 114.75, 114.79, 115.53, 115.65, 122.34, 128.50, 128.66, 130.11, 131.29, 131.81, 132.14, 135.64, 139.88, 140.72, 153.08, 154.06, 170.25, MS *m*/*z* 404 (M$^+$). Anal. Calcd for $C_{24}H_{24}N_2O_4$: C, 71.27; H, 5.98; N, 6.93. Found: C, 71.29; H, 5.96; N, 6.91.

Acknowledgements

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