An Efficient Synthesis of Optically Active *trans*-(3*R*,4*R*)-3-Acetoxy-4-aryl-1-(chrysen-6-yl)azetidin-2-ones Using (+)-Car-3-ene as a Chiral Auxiliary

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An efficient enantioselective synthesis of 3-acetoxy *trans*-β-lactams **7a** and **7b** *via* [2+2] cycloaddition reactions of imines **4a** and **4b**, derived from a polycyclic aromatic amine and bicyclic chiral acid obtained from (+)-car-3-ene, is described. The cycloaddition was found to be highly enantioselective, producing only *trans*-(3*R*,4*R*)-*N*-azetidin-2-one in very good yields. This is the first report of the synthesis of enantiomerically pure *trans*-β-lactams **7a** and **7b** with a polycyclic aromatic substituent at N(1) of the azetidin ring.

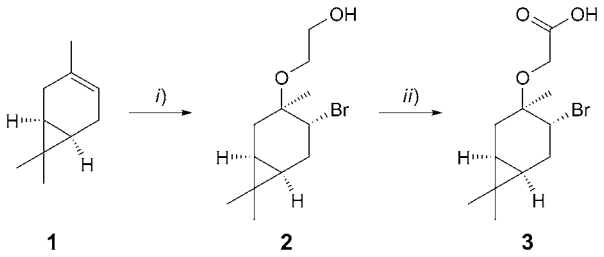
Introduction. – The β-lactam skeleton is the key structural unit responsible for the antibacterial property of the most widely employed antibiotics [1]. The resistance developed by the microorganisms against the β-lactam drugs maintained the interest of organic chemists for the development of new β-lactams with broader antibacterial activity [2]. As a consequence, several synthetic methods for β-lactams are now available, and the topic has been extensively reviewed [3]. The most convenient procedure for the synthesis of the β-lactam ring skeleton is the [2+2] cycloaddition of ketenes to imines, known as the *Staudinger* cycloaddition [4]. In particular, this method has provided useful and economical entries to β-lactams, mainly due to the ready availability of both imines and ketenes; however, the subject still continues to be an active area of research [5]. Over the past few years, asymmetric versions of this reaction have been developed using a combination of either chiral ketenes and achiral imines, or achiral ketenes and chiral imines, generally providing good diastereoselectivity [6].

In the diastereoselective synthesis of β-lactams, chiral starting materials such as aldehydes, acids/acid halides, and amines have been widely used. High levels of stereoselection were achieved, when the β-C-atom of the chiral aldehyde is attached to a heteroatom [7]. In recent years, several researchers have studied different approaches to optically pure β-lactams of predictable absolute configuration [8][9]. *Deshmukh* and co-workers [10] have reported that the reaction of an acid chloride (or equivalent) with a *Schiff* base derived from an optically active aldehyde and an achiral amine, in the presence of Et_3N, leads to a very high level of diastereoselectivity. In some cases, a single, optically pure, *cis*-β-lactam was obtained [10d][10e][10f]. We describe here the synthesis of optically pure *trans*-β-lactams with a polyaromatic substituent at N(1) of the azetidin-2-ones derived from (+)-car-3-ene.

Results and Discussion. – In continuation of our endeavor for the synthesis and biological evaluation of novel anticancer β-lactams, we have synthesized racemic *trans*-

β-lactams from polycyclic aromatic imines and other imines [11]. A preliminary structure–activity study has revealed that *trans*-1-*N*-chrysenyl and 1-*N*-phenanthrenyl 3-acetoxy-4-arylazetidin-2-ones have potent, selective anticancer activities [11]. We have also studied the diastereoselectivity of β-lactam formation with imines which have *N*-polycyclic aromatic substituents. Our research has revealed that functionalized β-lactams in racemic and optically active forms can be prepared by simple methods [11]. Therefore, we envision that enantiomerically pure *trans*-1-chrysenyl- and 1-phenanthrenyl substituted 3-acetoxy-4-aryl-2-azetidinones would have higher anticancer activities than their racemic forms. Also, there is no methodology reported to synthesize chiral *trans*-β-lactams *via* a chiral ketene derived from a natural terpenoid. With this background information, we have synthesized a bicyclic chiral acid **3** derived from readily available and naturally abundant (+)-car-3-ene (**1**) [12]. (+)-Car-3-ene (**1**), on reaction with NBS [13] in the presence of ethylene glycol, afforded bromo alcohol **2** in moderate yield. Oxidation of **2** gave the bicyclic chiral acid **3** in excellent yield (*Scheme 1*).

Scheme 1



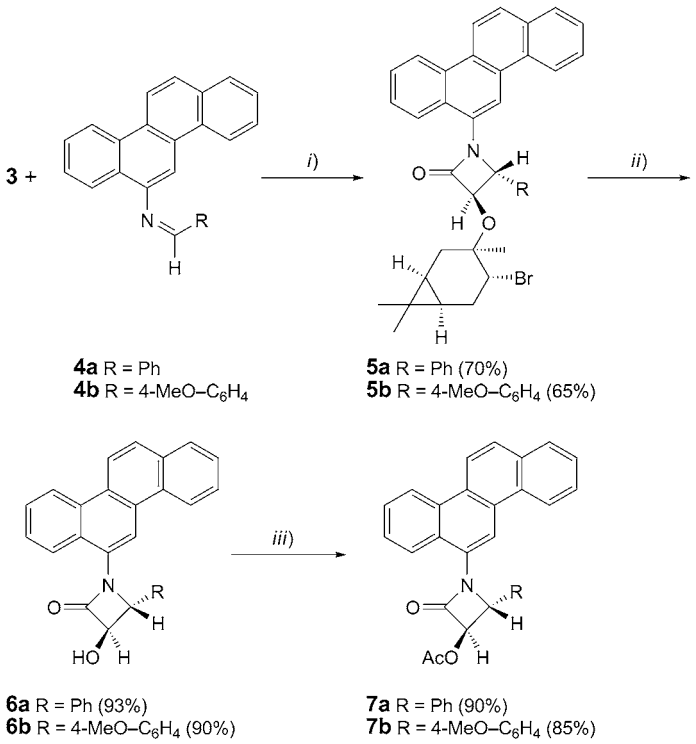
i) *N*-Bromosuccinimide (NBS)/$HOCH_2CH_2OH$, 0°, 4 h. *ii*) CrO_3/acetone.

The *Staudinger* cycloaddition of **3** with imines **4a** and **4b** in the presence of Et_3N and *Mukaiyama*'s reagent (2-chloro-1-methylpyridinium iodide) as an acid activator [14] was performed. The progress of the reaction was monitored by TLC. The ^{1}H-NMR spectra of the crude products indicated the formation of *trans*-β-lactams **5a** and **5b**, respectively, in good yield (*Scheme 2*). No trace of the *cis*-isomer was detected by ^{1}H-NMR. The yield of the products was very good. The crude compounds were purified by flash column chromatography to give pure *trans*-β-lactams **5a** and **5b**, respectively, as white solids. The results described here are highly remarkable, as the preparation of a single optically active *trans*-β-lactam starting from a ketene has so far been unknown.

The stereochemical outcome and structure of **5a** was established by IR and NMR spectroscopy. The pure diastereoisomer **5a** showed a characteristic absorption band at 1766 cm^{-1} for the β-lactam C=O group. The ^{1}H-NMR spectra showed *doublet*s at 4.95 and 5.48 ppm for H–C(4) and H–C(3) of the β-lactam ring, respectively. The coupling constant, *J*, of these two *doublet*s is 1.95 Hz, which confirmed the *trans*-configuration for the β-lactam ring of **5a**. The signals in the aliphatic region at 0.67 – 2.48 ppm confirmed the presence of the (+)-car-3-ene moiety. The peak observed at 166.8 ppm in the ^{13}C-NMR spectra corresponds to the C=O group.

The cleavage of the chiral auxiliary was accomplished by reacting pure diastereoisomers **5a** and **5b** with Zn/AcOH under reflux for 12 – 15 h to give the corresponding

Scheme 2



i) Dry Et_3N, dry CH_2Cl_2, 2-chloro-1-methylpyridinium iodide, 0° to r.t., 15 h. *ii*) Zn/AcOH/MeOH, reflux, 4 h. *iii*) AcCl, Et_3N, anh. CH_2Cl_2, 0° to r.t., 15 h.

enantiomerically pure 3-hydroxy *trans*-β-lactams **6a** and **6b**, respectively, in excellent yields (*Scheme 2*). Their formation was confirmed by their spectroscopic data (^{1}H- and ^{13}C-NMR). Further, 3-hydroxy *trans*-β-lactams **6a** and **6b** on reaction with AcCl and Et_3N gave 3-acetoxy *trans*-β-lactams **7a** and **7b**, respectively, again in excellent yield. The structure **7a** and **7b** was established by spectroscopic and analytical data. The absolute configuration of β-lactam **7a** was assigned on the basis of its optical rotation and melting point in comparison with those of an authentical sample of **7a**, which was prepared earlier in our laboratory by a different method [11h][11m]. The optical rotation for **7a** was $[\alpha]_D^{20.1} = -39.62$ ($c = 0.12$, $CHCl_3$). The absolute configuration of **7a** was also confirmed by a comparison with known *trans*-β-lactams described earlier with respect to optical rotation and NMR data in the presence of a chiral shift reagent [11h][11m][15].

In summary, we have synthesized enantiomerically pure 3-acetoxy *trans*-β-lactams **7a** and **7b** in excellent yield. This is the first protocol to synthesize 3-acetoxy *trans*-β-lactams *via* (+)-car-3-ene as a chiral precursor. Moreover, the resulting optically active β-lactam should exhibit anticancer activity based on our previous work.

Experimental Part

General. Anal. grade chemicals (*Sigma–Aldrich*) were used. Silica gel (SiO_2) was used for column chromatography (CC). Deionized H_2O was used for the preparation of all aq. solns. M.p.: *Fisher Scientific electrochemical Mel-Temp** manual melting point apparatus (*Model 1001*). Optical rotations: *Rudolph Polarimer*. FT-IR Spectra: *Bruker IFS 55 Equinox* FT-IR spectrophotometer, as KBr discs. ^{1}H-(300 MHz) and ^{13}C-NMR (75.4 MHz) spectra: at r.t., *JEOL Eclipse-300* equipment with TMS as internal standard and $CDCl_3$ as solvent.

*2-{[(1*S*,3*R*,4*R*,6*R*)-4-Bromo-3,7,7-trimethylbicyclo[4.1.0]hept-3-yl]oxy}ethanol* (**2**). To a stirred soln. of *(+)-car-3-ene* (**1**; 1.36 g, 10 mmol) and ethylene glycol (31 ml, 50 mmol) in CH_2Cl_2 (30 ml), powdered NBS (2.23 g, 12.5 mmol) was added in small portions during 30 min at 0°. The mixture was allowed to warm to r.t. and stirred for a further 4 h. After completion of the reaction (TLC), cold H_2O (50 ml) was added to the mixture, which was extracted with CH_2Cl_2 (3 × 30 ml). The combined extracts were washed with sat. $NaHSO_3$ (15 ml), H_2O (20 ml), and brine (15 ml), dried (anh. Na_2SO_4), and filtered. The filterate was concentrated under reduced pressure, and the residue was purified by CC (SiO_2, 120 mesh; 10% AcOEt/hexane) to give 1.24 g (45%) of **2**. Pale-yellow liquid. $[\alpha]_D^{20} = -33.45$ ($c = 1.65$, $CHCl_3$). ^{1}H-NMR ($CDCl_3$): 0.65–0.90 (*m*, 2 H); 0.97 (*s*, 3 H); 1.00 (*s*, 3 H); 1.30–1.50 (*m*, 1 H); 1.35 (*s*, 3 H); 2.05–2.25 (*m*, 1 H); 2.40–2.50 (*m*, 2 H); 3.40–3.60 (*m*, 2 H); 3.65–3.75 (*m*, 2 H); 4.07 (*t*, *J* = 8, 1 H). ^{13}C-NMR ($CDCl_3$): 15.48; 17.70; 18.32; 19.50; 21.63; 28.39; 29.97; 31.80; 59.92; 61.83; 62.04; 75.25.

*2-{[(1*S*,3*R*,4*R*,6*R*)-4-Bromo-3,7,7-trimethylbicyclo[4.1.0]hept-3-yl]oxy}acetic acid* (**3**). To a stirred soln. of **2** (276 mg, 1 mmol) in acetone (10 ml), *Jones* reagent was added dropwise at 0° until decolorization of the reagent stopped. The mixture was further stirred for 3 h at r.t., the green precipitate of the chromium salt was filtered off, and the excess reagent was destroyed by adding i-PrOH at 0°. The soln. was concentrated under vacuum, and the residue was extracted with Et_2O (3 × 20 ml). The Et_2O extract was washed with brine and dried (Na_2SO_4). It was then filtered, and the filtrate, on concentration under reduced pressure, afforded **3** (232 mg, 80%). Pure product was obtained by crystallization from hexane/AcOEt to give **3** as white crystals. M.p. 85°. $[\alpha]_D^{20} = -72$ ($c = 0.45$, $CHCl_3$). ^{1}H-NMR ($CDCl_3$): 0.65–0.90 (*m*, 2 H); 0.98, 1.00 (2*s*, 6 H); 1.40 (*s*, 3 H); 1.3–1.4 (*m*, 1 H); 2.20 (*dd*, *J* = 5.5, 10, 1 H); 2.35–2.55 (*m*, 2 H); 4.00 (*m*, 1 H); 4.05 (*d*, *J* = 18, 1 H); 4.10 (*d*, *J* = 18, 1 H); 7.30–9.0 (br. *s*, 1 H). ^{13}C-NMR ($CDCl_3$): 15.71; 17.34; 18.18; 19.55; 21.85; 28.57; 30.88; 31.99; 59.74; 59.89; 78.12; 160.00.

trans-*β-Lactam* **5a**. To a stirred soln. of chrysene-1-imine **4a** (0.434 g, 1.31 mmol), **3** (0.384 g, 1.31 mmol), and Et_3N (0.54 ml, 3.93 mmol) in dry CH_2Cl_2 (20 ml), a soln. of 2-chloro-1-methylpyridinium iodide (0.402 g, 1.57 mmol) in dry CH_2Cl_2 (20 ml) was added dropwise at 0° during 1 h. The mixture was allowed to warm to r.t. and stirred overnight. The mixture was then diluted with CH_2Cl_2 (20 ml), and washed successively with H_2O (30 ml), sat. $NaHCO_3$ (30 ml), and brine (25 ml), and was dried (anh. Na_2SO_4). The solvent was removed by distillation under reduced pressure, and CC (SiO_2, 120 mesh; 10% AcOEt/hexane) of the residue gave **5a** (0.560 g, 70%) as white solid. Following a similar procedure, we have also obtained *trans-β*-lactam **5b** (0.702 g, 65%).

*(3*R*,4*R*)-3-{[(1*S*,3*R*,4*R*,6*R*)-4-Bromo-3,7,7-trimethylbicyclo[4.1.0]hept-3-yl]oxy}-1-(chrysen-6-yl)-4-phenylazetidin-2-one* (**5a**). White solid. M.p. 209–210°. R_f (10% AcOEt/hexane) 0.55. $[\alpha]_D^{20.1} = +59.60$ ($c = 0.33$, $CHCl_3$). IR (KBr): 1388, 1650, 1704, 1766. ^{1}H-NMR (300 MHz, $CDCl_3$): 0.67–0.97 (*m*, 2 H); 0.97 (*s*, 3 H); 1.5 (*s*, 3 H); 1.36–1.58 (*m*, 1 H); 2.22–2.43 (*m*, 1 H); 2.43–2.48 (*m*, 2 H); 4.01–4.05 (*m*, 4 H); 4.95 (*d*, *J* = 1.95, H–C(4)); 5.48 (*d*, *J* = 1.95, H–C(3)); 7.24–8.61 (*m*, 14 arom. H). ^{13}C-NMR (300 MHz, $CDCl_3$): 18.0; 20.0; 21.3; 28.6; 32.0; 58.4; 66.8; 81.0; 114.2; 118.0; 120.0; 122.2; 123.4; 125.7; 126.8; 126.8; 127.5; 127.7; 131.5; 136.3; 166.9.

*(3*R*,4*R*)-3-{[(1*S*,3*R*,4*R*,6*R*)-4-Bromo-3,7,7-trimethylbicyclo[4.1.0]hept-3-yl]oxy}-1-(chrysen-6-yl)-4-(4-methoxyphenyl)azetidin-2-one* (**5b**). White solid. M.p. 208–209°. R_f (20% AcOEt/hexane) 0.48. ^{1}H-NMR (300 MHz, $CDCl_3$): 0.67–0.98 (*m*, 2 H); 0.99 (*s*, 6 H); 1.51 (*s*, 3 H); 1.26–1.59 (*m*, 1 H); 2.05–2.23 (*m*, 1 H); 2.44–2.47 (*m*, 2 H); 3.66 (*s*, 3 H); 4.06–4.16 (*m*, 4 H); 4.96 (*d*, *J* = 1.90, H–C(4)); 5.43 (*d*, *J* = 1.90, H–C(3)); 6.77–8.72 (*m*, 13 arom. H). ^{13}C-NMR (300 MHz, $CDCl_3$): 18.1; 18.4; 20.0; 28.4; 28.7; 32.1; 55.1; 58.6; 66.0; 82.0; 114.3; 114.7; 121.0; 122.0; 126.7; 127.4; 127.6; 127.9; 128.1; 128.2; 159.9; 167.0.

*(3*R*,4*R*)-1-(Chrysen-6-yl)-3-hydroxy-4-phenylazetidin-2-one* (**6a**). To a soln. of **5a** (0.189 g, 0.312 mmol) in MeOH (5 ml), activated Zn (0.248 g, 3.75 mmol), and glacial AcOH (1.0 ml) were

added under stirring. The mixture was then heated to 80° with continuous removal of MeOH during 12 h. Then, MeOH was distilled to recover (+)-car-3-ene, and the residue was treated with CH_2Cl_2 (30 ml) and filtered; the solid was washed with CH_2Cl_2 (3 × 20 ml). The combined filtrate was successively washed with dil. HCl (5%, 10 ml), sat. $NaHCO_3$ (2 × 15 ml), H_2O (2 × 10 ml), brine (10 ml), and dried (anh. Na_2SO_4). The removal of the solvent gave **6a** (0.112 g, 93%). White solid. M.p.: 209–210°. R_f (30% AcOEt/hexane) 0.33. IR (KBr): 1388, 1650, 1745, 3400. ^{1}H-NMR (300 MHz, $CDCl_3$): 4.98 (*d*, *J* = 1.65, H–C(4)); 5.44 (*d*, *J* = 1.65, H–C(3)); 7.17–8.25 (*m*, 14 arom. H). ^{13}C-NMR (300 MHz, $CDCl_3$): 66.8; 82.0; 114.2; 118.0; 120.0; 122.2; 123.4; 125.7; 126.8; 126.8; 127.5; 127.7; 131.5; 136.3; 166.9.

*(3*R*,4*R*)-1-(Chrysen-6-yl)-3-hydroxy-4-(4-methoxyphenyl)azetidin-2-one* (**6b**). Pale yellow oil. R_f (30% AcOEt /hexane) 0.25. ^{1}H-NMR (300 MHz, $CDCl_3$): 4.21 (*s*); 4.98 (*d*, *J* = 1.65, H–C(4)); 5.39 (*d*, *J* = 1.65, H–C(3)); 6.72–8.22 (*m*, 13 arom. H). ^{13}C-NMR (300 MHz, $CDCl_3$): 55.1; 68.1; 68.2; 115.0; 119.5; 121.0; 128.6; 128.9; 130.7; 130.9; 131.1; 132.5; 148.0; 149.4; 161.5; 163.2; 167.8.

*(3*R*,4*R*)-1-(Chrysen-6-yl)-2-oxo-4-phenylazetidin-3-yl Acetate* (**7a**). To a soln. of **6a** (0.073 g, 0.187 mmol) in CH_2Cl_2 (5 ml), Et_3N (0.023 ml, 0.375 mmol) and AcCl (0.052 ml, 0.375 mmol) were added at 0°, and the mixture was kept at r.t. for 30 min. Then, the mixture was diluted with CH_2Cl_2, and washed with sat. $NaHCO_3$ and H_2O to give a crude pale-yellow solid. The crude compound was purified by flash CC (20% AcOEt/hexane) to give pure **7a** (0.072 g, 90%). White solid. Recrystallization from CH_2Cl_2/hexane gave white needles. M.p.: 262–263°. R_f (20% AcOEt/hexane) 0.54. $[\alpha]_D^{20.1} = -39.62$ (*c* = 0.12, $CHCl_3$). IR (KBr): 1255, 1660, 1755. ^{1}H-NMR (300 MHz, $CDCl_3$): 2.28 (*s*); 5.53 (*d*, *J* = 1.92, H–C(4)); 5.76 (*d*, *J* = 1.92, H–C(3)); 7.24–8.64 (*m*, 14 arom. H). ^{13}C-NMR (300 MHz, $CDCl_3$): 65.2; 68.6; 81.0; 115.7; 124.6; 127.4; 129.29; 129.8; 130.9; 138.8; 169.8; 182.3.

*(2*R*,3*R*)-1-(Chrysen-6-yl)-2-(4-methoxyphenyl)-4-oxoazetidin-3-yl Acetate* (**7b**). Compound **7b** was prepared by the method as described for **7a**. Recrystallization from CH_2Cl_2/hexane. White solid. M.p. 180–181°. R_f (20% AcOEt/hexane) 0.45. $[\alpha]_D^{20.1} = -45.04$ (*c* = 0.10, $CHCl_3$). ^{1}H-NMR (300 MHz, $CDCl_3$): 2.29 (*s*); 3.68 (*s*); 5.48 (*d*, *J* = 1.92, H–C(4)); 5.75 (*d*, *J* = 1.92, H–C(3)); 6.78–8.63 (*m*, 13 arom. H). ^{13}C-NMR (300 MHz, $CDCl_3$): 55.2; 65.6; 80.9; 114.3; 115.2; 117.3; 120.0; 122.2; 123.5; 124.7; 127.1; 128.0; 130.1; 132.3; 160.3; 163.3; 167.9; 170.2.

We gratefully acknowledge the funding support from the *NIH-SCORE* (Grant No. 2S06M008038-37).

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Received June 2, 2011