Pergamon

Tetrahedron Letters, Vol. 38, No. 21, pp. 3691-3694, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)00714-4

Reversal of Expected Stereochemical Outcome in the Oppolzer Reaction of a Cyclic N-Enoylsultam: Enantioselective Synthesis and Absolute Configuration of Antispermatogenic Hexahydroindeno[1,2-c]pyridines

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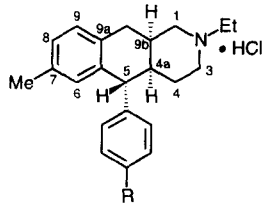
ABSTRACT: p-Tolylmagnesium bromide added with high enantioselectivity to a cyclic enoylsultam (**4**), but the diastereofacial selectivity (determined by X-ray crystallography of the product) was opposite that reported for acyclic enoylsultams. The reaction was used in an enantioselective synthesis of antispermatogenic hexahydroindenopyridines and allowed the absolute configuration of the active enantiomer (**1**) to be determined. © 1997 Elsevier Science Ltd.

The (4a*RS*,5*SR*,9b*RS*) hexahydroindeno[1,2-c]pyridines **1a** (Sandoz 20,438[2]), **1b** (RTI 4587-054) and **1c** (RTI 4587-056)[3] are potent, orally active antispermatogenic compounds. The activity resides essentially in one enantiomer.[3] In carrying out an enantioselective synthesis of these compounds and the determination of their absolute configuration, we have found that the Oppolzer reaction (asymmetric 1,4-addition of a Grignard reagent to an N-enoylsultam)[4] with the N-camphorsultam derivative of N-ethyl-1,2,5,6-tetrahydropyridine-4-carboxylic acid (**4**) gave an opposite configuration to that predicted from results[4] with acyclic unsaturated acids.

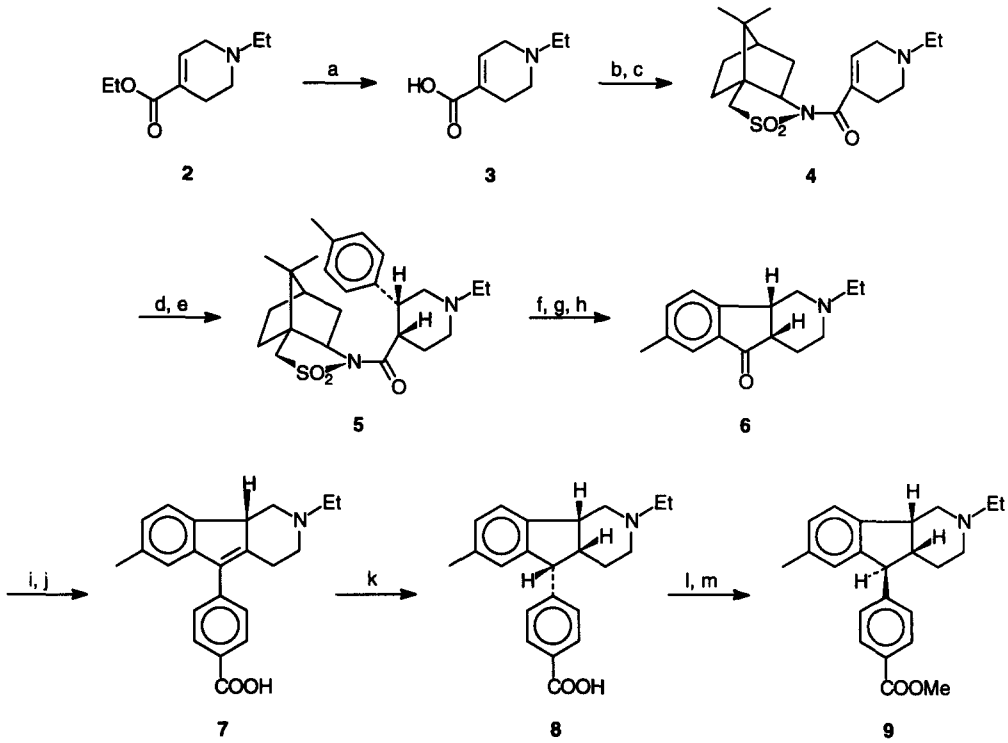


1a, R = Me
1b, R = COOH
1c, R = COOMe

p-Tolylmagnesium bromide was added to the chiral enoylsultam **4** derived from 1*S*(-)-2,10-camphorsultam to yield **5** (Scheme 1).[5] The crude product was hydrolyzed, converted to the acid chloride and cyclized under Friedel-Crafts conditions to the ketone **6**. Compound **6** was obtained in 92% overall enantiomeric excess, as shown by HPLC [chiral Sumitomo OA-4900 column eluted with hexane, dichloroethane, ethanol, trifluoroacetic acid (44.0:53.7:2.2:0.1, v:v) at 1.9 mL/min and analyzed by absorbance at 254 nm].

Recrystallization of crude **5** from ether:hexane gave the pure sultam enantiomer **5** in 66% yield (52% overall from **2**), which was converted to ketone **6**.[6] The latter was shown by HPLC to be a single enantiomer. Thus, as expected, no racemization occurred during the steps leading from **5** to **6**. Recrystallization of **5** from ether gave crystals suitable for X-ray analysis.[7] The absolute configuration is shown in Figure 1 and demonstrates that the aryl residue is cis to the acylsultam group and that the 1*S*-enoylsultam **4** resulted in the *R*-configuration at C-3 of conjugate addition product **5**.

Scheme I

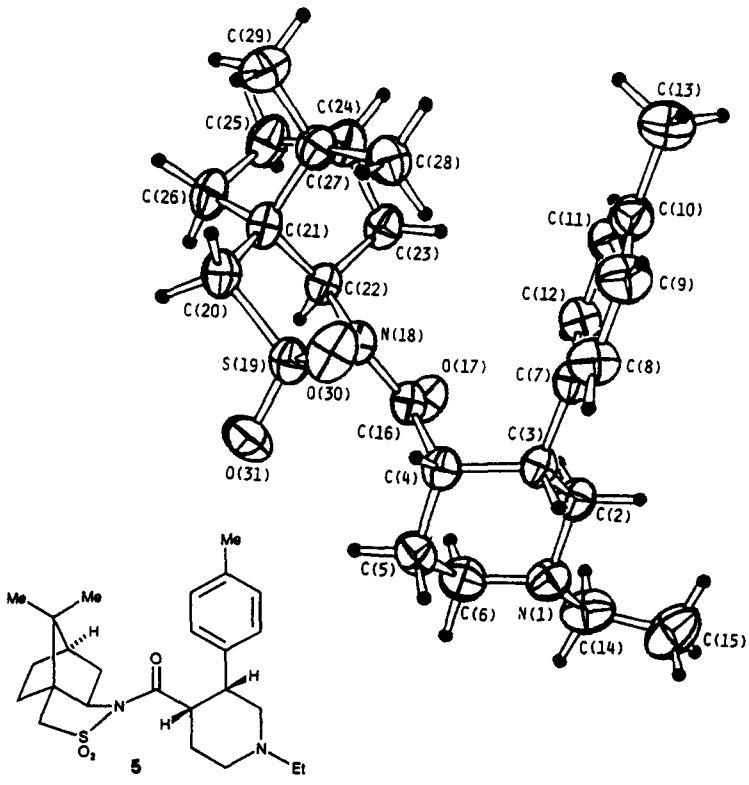


2 3 4 5 6 7 8 9

a) HCl/H_2O
b) $SOCl_2$
c) *S*(-)-2,10-camphorsultam, n-BuLi
d) 2 mols p-tolylmagnesium bromide
e) aq, NH_4Cl
f) LiOH
g) $SOCl_2$
h) $AlCl_3$
i) p-bromobenzoic acid, n-BuLi
j) HCl/H_2O
k) H_2/catalyst
l) KOH, *n*-BuOH, reflux
m) MeOH, $SOCl_2$

The configuration of **5** at the carbon bearing the aryl substituent is the opposite of that normally associated with the reaction of analogous acyclic α,β-disubstituted enoylsultams with Grignard reagents.[4] This could be due to the presence of the basic nitrogen in the tetrahydropyridine ring, which by coordination with a molecule of Grignard reagent could influence the direction of delivery of the aryl group, or to a change in the favored stereochemistry of the transition state when the double bond is part of a 6-membered ring.[8] Present data do not allow a choice between these two possibilities.

Figure 1: ORTEP Diagram of Compound 5



Ketone **6** was converted to the hexahydroindenopyridine **1b** by treatment with the aryl lithium reagent derived from p-bromobenzoic acid, dehydration to the olefin **7**, catalytic reduction and base-catalyzed epimerization at C-5 as previously described.[3] Esterification led to the methyl ester **1c**. Partial racemization occurred during the catalytic reduction, probably due to double bond migration to the 4a,9-position. The degree of racemization was dependent on temperature and catalyst. It ranged from complete racemization with $PdCl_2$/$NaBH_4$/3 atm H_2 at 55° to 73% ee at 23°; but with Pt/C/H_2 the ee at 60° was comparable to that at 23° (67% and 70%, respectively). Comparison by chiral HPLC with the enantiomers of **1c** obtained previously by resolution[3] showed that the enoylsultam **4** from 1*S*(-)-2,10 camphorsultam led to the inactive enantiomer of **1c** having a positive rotation at the sodium D line in chloroform.

Since C-3 of conjugate addition product **5** becomes the 9b-carbon of the indenopyridines **1** and the relative position of the hydrogens has been established,[3] this establishes the absolute configuration of the inactive enantiomer of **1c** as 4a*R*,5*S*,9b*R*. The antispermatogenic enantiomers of **1b** and **c** therefore have the 4a*S*,5*R*,9b*S* configuration shown in structure 1.

Acknowledgment: This work was supported by Contract No. N01-HD-3-3179 with the Contraceptive Development Branch, NICHD.

References and Notes

1. Present address for Joseph M. Jump is Hoechst Celanese Corporation, Coventry Technical Center, 500 Washington St., Coventry, RI 02816.

2. Suter, K.E.; Hodel, C.; Gradient, F. *Experientia* **1977**, *30*, 810.
3. Cook, C.E.; Wani, M.C.; Jump, J.M.; Lee, Y.-W.; Fail, P.A.; Anderson, S.A.; Gu, Y.-Q.; Petrow, V. *J. Med. Chem.* **1995**, *38*, 753-763.
4. Oppolzer, W.; Poli, G.; Kingma, A. J.; Starkemann, C.; Bernardinelli, G. *Helv. Chim. Acta* **1987**, *70*, 2201-2214.
5. Ester **2**[3] was refluxed 4 h with 1.5 M HCl. The solution was evaporated and the residue recrystallized from methanol to give the hydrochloride of acid **3**, mp. 265° C (dec). This compound (6.79 mmol) was refluxed 2 h with 15 mL of thionyl chloride. After evaporation of $SOCl_2$ and 3 evaporations with toluene, to the residue was added a solution of lithium 1*S*-2,10-camphorsultam (15 mmol n-BuLi in 15 mL hexane added to 14.7 mmol camphorsultam in 30 mL tetrahydrofuran). Stirring at room temperature was carried out for 18 h before addition of saturated NH_4Cl and concentration. Camphorsultam was extracted by ether from an HCl solution of the residue. Basification (NH_4OH) and reextraction yielded crude **4**, which was recrystallized from n-hexane [1.9 g, 79%, mp. 120°C, $[\alpha]_D^{21}$ -74.8 (c=1.0, $CHCl_3$]. To **4** (16 mmol) in toluene (200 mL) at -78° was added p-tolylmagnesium bromide (33.6 mL of 1M solution in ether) over 10 min. After 30 more minutes at -78°, overnight at -10° and 2 h at 5°, the reaction was quenched with saturated NH_4Cl. Acid-base partition gave crude solid **5** (7.12 g, 100%), recrystallized from ether:hexane (1:2) to give pure **5** [4.68 g, 66%, m.p. 150.5-151.7°, $[\alpha]_D^{21}$ -26.2 (c=1.14, $CHCl_3$)].
6. Sultam **5** (15.45 mmol) and LiOH (153 mmol) were stirred and refluxed in tetrahydrofuran (40 mL) and water (40 mL) for 26 h. The solution was cooled (5°), acidified to pH 0 (HCl), evaporated and dried in vacuo. $SOCl_2$ (15 mL) was added at 5° and the solution stirred at room temperature for 4 h. Evaporation in vacuo was followed by reevaporation with 1,2-dichloroethane. The residue was stirred for 1 h at 35-40° with $AlCl_3$ (40 mmol) and dichloroethane (25 mL), worked up as usual and distilled in a Kugelrohr apparatus to yield ketone **6**, $[\alpha]_D^{20}$ +95.9 (free base, c=1.2, $CHCl_3$), $[\alpha]_D^{19}$ +71.9 (HCl salt, c=1.1, $CHCl_3$).
7. *Crystal data for* **5**: $C_{25}H_{36}N_2O_3S$, M = 444.64, monoclinic, space group $P2_1$(no. 4), a = 10.001(1) Å, b = 24.854(2) Å, c = 9.849(1) Å, b = 97.19(1)°, V = 2428.9(7) Å^3, Z =4, $D_{calcd.}$ = 1.216 g cm^{-3}, μ(Cu-*K*a radiation, λ = 1.5418 Å) = 13.6 cm^{-1}. Intensity data (+*h*,+*k*, ±*l*; 5107 non-equivalent reflections, $\theta_{max.}$ = 75°) were recorded on an Enraf-Nonius CAD-4 diffractometer [Cu-*K*α radiation, graphite monochromator; w-2θ scans, scanwidth (0.85 + 0.14tanθ)°] from a crystal of dimensions 0.36 x 0.38 x 0.46 mm. The crystal structure was solved by direct methods. The asymmetric unit consists of two crystallographically, but conformationally similar, molecules. Full-matrix least-squares refinement of atomic positional and thermal parameters (anisotropic C, N, O, S; fixed H contributions) converged (max. shift:esd = 0.03) at R = 0.039 (R_w = 0.055) over 4356 absorption-corrected [$T_{max.}$:$T_{min.}$(rel.) = 1.00:0.94] reflections with I > 3.0s(I). Atomic parameters, bond lengths, bond angles and torsion angles have been deposited at the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.
8. The ground state (GS) conformation of **4** undoubtedly has a twisted C=C-C=O conformation (see discussion in Kim, B.H.; Curran, D.P. *Tetrahedron* **1993**, *49*, 293-318). If the S-O_α and C=O are constrained to be *syn* by chelation with magnesium, a *cisoid* transition state would require that the aryl moiety be delivered from the top face of the molecule, probably by coordination of a second molecule of aryl Grignard with the amine nitrogen. A *transoid* transition state would allow the mechanism of Oppolzer (reference 4) to apply.

(*Received in USA* 20 *December* 1996; *revised* 4 *April* 1997; *accepted* 6 *April* 1997)