Enantioselective Synthesis of the Carbapenem Ring System from (*S*)-Proline

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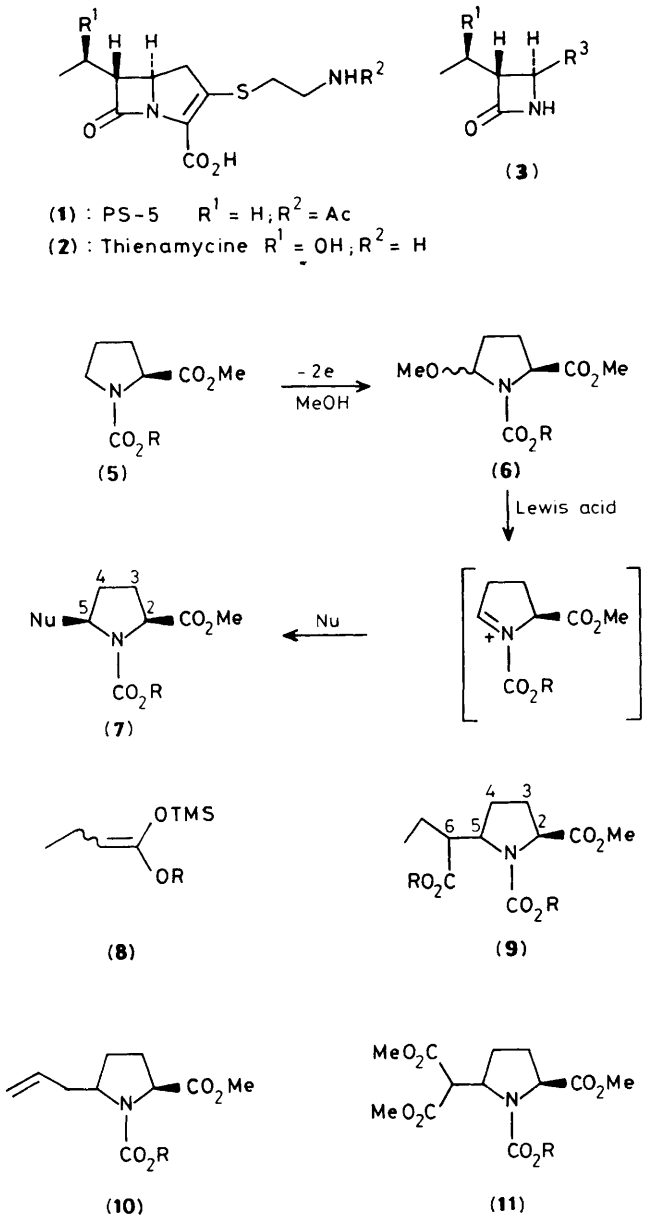
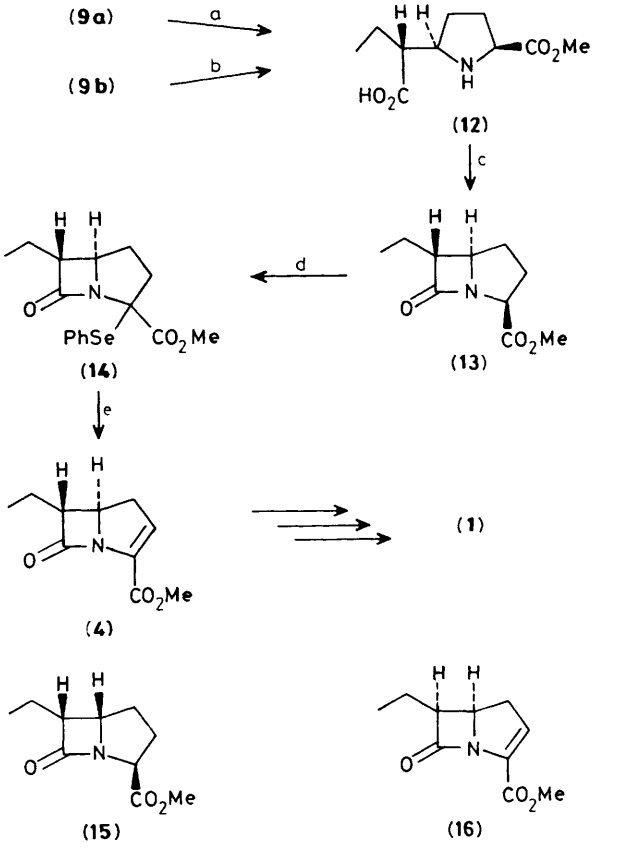
Enantioselective synthesis of (+)-PS-5 *via* stereoselective alkylation of proline derivatives is described.

Carbapenems, a new class of β-lactam antibiotics, have been of considerable interest to many synthetic chemists during the past decade owing to their potency against a wide variety of pathogenic micro-organisms and low productivity in the process of fermentation.[1] Hundreds of studies have been reported in the quest for new synthetic approaches to carbapenems,[2] but in most reports, attention was focused on the stereospecific synthesis of 4-azetidinone derivatives (**3**) which were eventually transformed into a carbapenem ring system.[3]



Scheme 1. For (5)—(11) **a**; R = CH_2Ph, **b**; R = Bu^t.



Scheme 2. *Reagents*: a, H_2 (4 atm.)—5% Pd/C, MeOH, room temp., 2 h (quant.); b, 4 M–HCl/dioxane, overnight (quant.); c, dicyclohexylcarbodiimide, MeCN, room temp., overnight (66%); d, lithium hexamethyldisilazide (2.5 equiv.), PhSeCl (3.0 equiv.), tetrahydrofuran (THF) (68%); e, *m*-chloroperbenzoic acid (2 equiv.), CH_2Cl_2, −30 °C → room temp. (61%).

We have planned a new synthetic route to carbapenems using (*S*)-proline as a chiral and inexpensive starting material. Here we describe an enantioselective synthesis of the carbapenem ring system (**4**), which is the precursor to (+)-PS-5.[4]

For this route to carbapenems, the first aim was to introduce a 1-carboxypropyl group to the 5-position of the proline ring with (5*R*)-configuration, because it is of great importance that β-lactams have the (5*R*)-configuration for them to be antimicrobial agents. We have thus examined the Lewis acid-promoted alkylation of the C-5-position of proline derivatives (**6**), using the C-2-methoxycarbonyl group as a convenient handle for stereoselection. Compound (**6**) was easily obtained from the proline derivative (**5**) by anodic oxidation.[5]

The results are summarized in Table 1. Though we have already found that cobalt catalysed amidocarbonylation of 5-methoxy proline derivatives gives *trans*-pyrrolidine dicarboxylic acid derivatives,[6] addition of nucleophiles to (**6**) with the aid of a Lewis acid proceeded with *cis*-selectivities.[7] Addition

Table 1. Addition of nucleophiles to (**6**).[a]

Substrate	Nucleophile	Product	Yield (%)	5*R*/5*S*[b]
(**6a**)	(**8a**)	(**9a**)	50	75/25
(**6a**)	Allyltrimethylsilane	(**10a**)	40	77/23
(**6a**)	Dimethyl malonate	(**11a**)	49	55/45
(**6b**)	(**8b**)	(**9b**)	55	77/23

[a] Solvent: CH_2Cl_2, Lewis acid: $TiCl_4$, under Ar. [b] Determined by ^1H n.m.r. spectroscopy.

of ketene silyl acetal to (**6**) gave pyrrolidine derivatives (**9**) having a β-carboxy group with the 5*R*-configuration (50%,† diastereoisomeric excess 50%). A similar selectivity was obtained in the addition reaction of allyltrimethylsilane, although the reaction with dimethylmalonate was non-stereoselective.

Compound (**9**) was found to be a 1 : 1 mixture of stereoisomers with the opposite configuration at C-6. It was easy to separate all isomers by using reverse-phase preparative h.p.l.c. [H_2O–MeOH 30 : 70, YMC-octadecylsilane (ODS)]. These results enabled us to use a natural amino acid (*S*)-Pro as a starting material for the synthesis of carbapenems.

† All the yields are values after purification with medium pressure liquid chromatography (Lobar column Si60, E. Merck).

The (5*R*,6*S*)-isomer of (**9**) was deprotected and cyclized to the β-lactam (**13**). The stereochemistry of (**13**) was determined from the coupling constant (3.0 Hz) between H-5 and H-6, and from the higher chemical shift for H-3, δ 3.88, compared to that, δ 4.39, of the 3,5-*cis*-carbapenem (**15**), derived from the (2*S*,5*S*)-isomer of (**9**). Compound (**13**) was converted to the carbapenem (**4**)‡ *via* the selenide (**14**). The optical purity of (**4**) was determined to be >98% by h.p.l.c. on a chiral stationary phase.§ We were also able to synthesize the 5,6-*cis*-carbapenem (**16**)‡ (which can be converted to 6-*epi*-PS-5) starting from the (5*R*,6*R*)-isomer of (**9**). Compound (**4**) is able to be transformed into (+)-PS-5 (**1**) by the methods reported by Southgate *et al.*[4] So, we have succeeded in the formal total synthesis of (+)-PS-5 starting from the readily available natural amino acid, (*S*)-proline.

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‡ (**4**): ^{1}H n.m.r. (300 MHz, $CDCl_3$) δ 1.05 (3H, t, 9-H), 1.88 (2H, m, 8-H), 2.76 (1H, ddd, 1-H), 2.93 (1H, ddd, 1-H), 3.13 (1H, ddd, J_{5-6} 3.0 Hz, 6-H), 3.84 (3H, s, OCH_3), 4.00 (1H, ddd, 5-H), 6.46 (1H, dd, 2-H); i.r. 1770 cm^{-1} (N–C=O), 1718 cm^{-1} (O–C=O); *m/z* 195.0926 (calc. for $C_{10}H_{13}NO_3$, 195.0892).

(**16**): ^{1}H n.m.r. δ 1.01 (3H, t, 9-H), 1.61 (1H, m, 8-H), 1.83 (1H, m, 8-H), 2.76 (2H, m, 1-H), 3.53 (1H, ddd, J_{5-6} 6.0 Hz, 6-H), 3.84 (3H, s, OCH_3), 4.53 (1H, ddd, 5-H), 6.52 (1H, dd, 2-H); i.r. 1765 cm^{-1} (N–C=O), 1720 cm^{-1} (O–C=O).

§ The chromatogram showed two peaks with R_t = 42.2 and 47.4 min in 98.8:1.2 ratio assignable to the (5*R*)- and (5*S*)-isomers, respectively.

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