

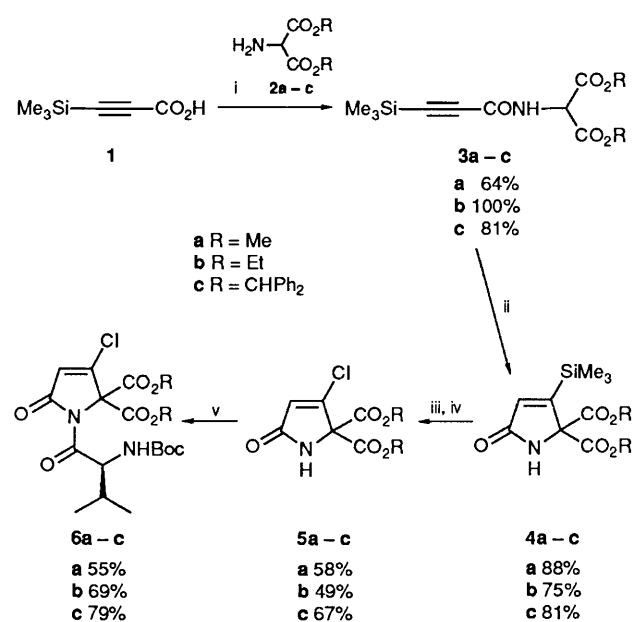
A Novel Chiral Oxycarbonyl Rearrangement

Nobuyoshi Yasuda† and Kazuo Sakane*

New Drug Research Laboratories, Fujisawa Pharmaceutical Co. Ltd., 2-1-6 Kashima, Yodogawaku, Osaka 532, Japan

A novel chiral oxycarbonyl rearrangement from carbon to nitrogen was observed and its mechanism is reported.

During a synthetic study towards the antibiotic FR900148,¹⁻³ we found a novel chiral oxycarbonyl rearrangement. The starting compounds **6a-c** for the rearrangement were prepared as shown in Scheme 1. Acylation of aminomalonates **2a-c** with trimethylsilylprop-2-ynoic acid **1**, followed by cyclization using modified Johnson conditions,⁴ gave the desired pyrrolidine derivatives **4a-c** in good yields. Treatment of **4a-c** with chlorine in the presence of *N*-chlorosuccinimide (NCS), followed by treatment with tetrabutylammonium fluoride in tetrahydrofuran (THF), gave the corresponding vinyl chloride derivatives **5a-c** in moderate yields. The structure of **5b**‡ was confirmed by single crystal X-ray analysis as shown in Fig. 1(a). *N*-acylation with *N*-Boc-L-valine (Boc = butoxycarbonyl) was carried out by the activated ester method to give the starting compounds **6a-c**.



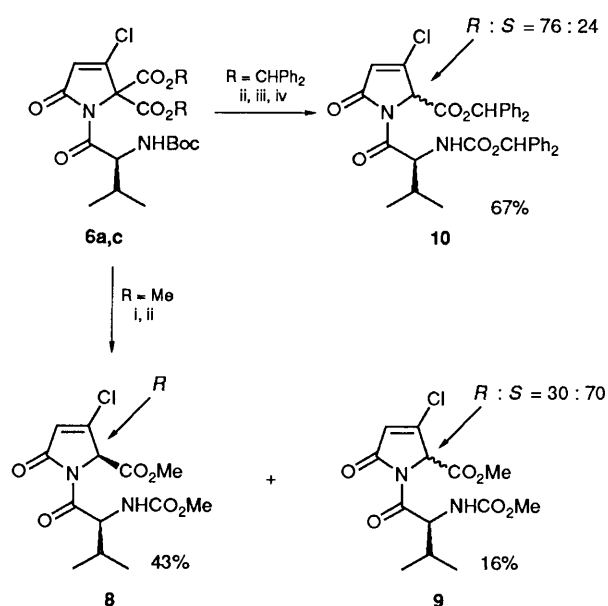
Scheme 1 Reagents and conditions: i, DCC (1.05 equiv.) in CH₂Cl₂; room temp. overnight; or DMF (1.3 equiv.), POCl₃ (1.3 equiv.), **1** (1 equiv.), in THF, 0 °C, 30 min; then **2b** (1 equiv.), in aq. THF, at pH 7-7.5, 0 °C, 30 min; ii, LiN(SiMe₃)₂ (1.1 equiv.), -78 °C, 20 min; then CuI (1.1 equiv.), TMEDA (1.2 equiv.), -78 °C, 20 min; then Me₃SiCl (1.2 equiv.), room temp. overnight; iii, Cl₂ (4 equiv.), NCS (1 equiv.), in CCl₄-CH₂Cl₂, 0 °C-room temp. 3.5 h; iv, Bu₄NF (2 equiv.), in THF, -78 °C, 20 min; v, NaH (1.2 equiv.), in THF, room temp. 3h; then Boc-L-Val-ONb⁵ (1.5 equiv.), room temp. (overnight), reflux (30 min), (DCC = dicyclohexylcarbodiimide, DMF = dimethylformamide, TMEDA = tetramethylethylenediamine, ONb = 5-norbornene-2,3-dicarboximidoxy)

† Present address: Process Research Labs., Merck Sharp & Dohme, PO Box 2000, Rahway, NJ 07065, USA

‡ Crystal data for: **5b** C₁₀H₁₂ClNO₅, monoclinic, *P*2₁/*c*, *M*_r = 261.66, *a* = 11.085(2), *b* = 7.634(1), *c* = 14.385(3) Å, β = 91.08(3)°, *V* = 1217.1(3) Å³, *Z* = 4, *D*_x = 1.429 g cm⁻³, *T* = 295 K. *R* = 0.075 after refinement of 158 parameters from 3678 independent reflections. **8** C₁₃H₁₇ClN₂O₆, monoclinic, *P*2₁, *M*_r = 332.74, *a* = 10.690(15), *b* = 9.647(3), *c* = 7.595(7) Å, β = 92.45(15)°, *V* = 782.5(14) Å³, *z* = 2, *D*_x = 348 g cm⁻³, *T* = 295 K. *R* = 0.105 after refinement of 199 parameters from 1905 independent reflections. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.

Novel chiral oxycarbonyl rearrangement from carbon to nitrogen occurred upon selective removal of the Boc moiety from **6a-c** as shown in Scheme 2. Treatment of **6a** with trifluoroacetic acid (TFA) in CH₂Cl₂ in the presence of anisole, followed by neutralization,§ gave spontaneously the *R*-ester **8** in 43% yield as crystals, whose structure was determined by single crystal X-ray analysis‡ as shown in Fig. 1(b). An inseparable mixture of *R*- and *S*-esters **9** was obtained from the mother liquors in 16% yield, for which the *R* and *S* ratio was 30:70 by HPLC; total selectivity of the *R*-ester **8** was 81% in 59% chemical yield. In the case of benzhydryl ester **6c**, deprotection was carried out with Me₃SiI. Neutralization followed by treatment with silica gel gave an inseparable *R,S* mixture **10** in 67% yield, for which the *R* and *S* ratio was determined as 76:24 by HPLC.

This reaction was initiated by nucleophilic attack of the primary nitrogen to the carbonyl carbons. Unusual carbon-carbon bond cleavage subsequently occurred to generate a



Scheme 2 Reagents and conditions: i, TFA, anisole, in CH₂Cl₂ room temp. 1.5 h; ii, extraction with EtOAc at pH 7.5; iii, Me₃SiI (1.5 equiv.), in CH₂Cl₂, 0 °C, 15 min; iv, silica gel, Et₂O, room temp. overnight

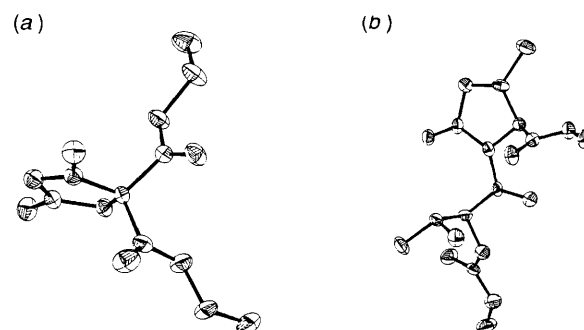


Fig. 1 (a) Single crystal X-ray structure of **5b**; (b) single crystal X-ray structure of **8**

§ The neutralization was necessary for the rearrangement.

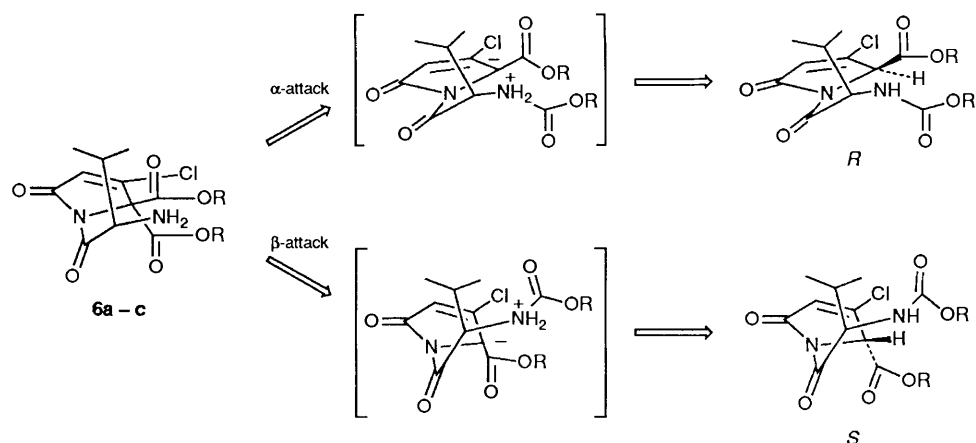


Fig. 2 Reaction pathway for novel oxycarbonyl rearrangement

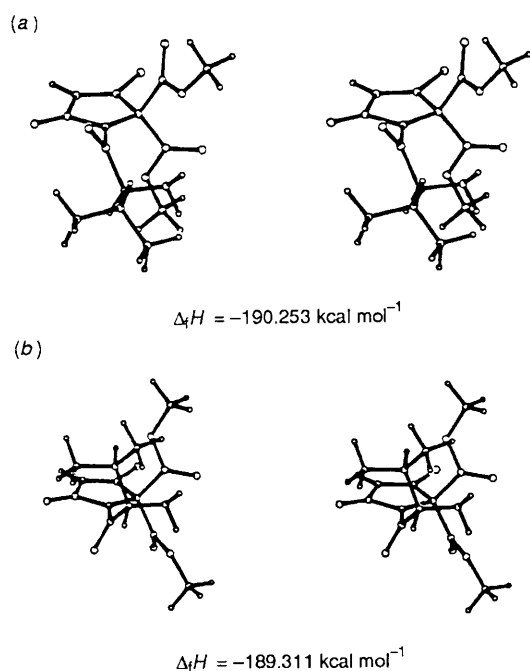


Fig. 3 (a) Stereoview of conformer A; (b) stereoview of conformer B (MNDO calculations)

highly stabilized carbanion, which would be immediately protonated from the resultant oxycarbonylammonium species, as shown in Fig. 2. Therefore, the stereochemistry at the newly formed chiral centre would be determined by the

orientation of nucleophilic attack of the free nitrogen. In order to determine this orientation, we attempted an MNDO conformational analysis. In the case of attack at the α -carbonyl carbon, a chair-like conformer (A), containing the bulky isopropyl moiety (Pr^i) in a pseudoequatorial orientation, is the most favoured conformation and leads to the R-ester. In the case of attack at the β -carbonyl carbon, a chair-like conformer (B) containing Pr^i in a pseudoaxial orientation is the preferred one and leads to the S-ester. Their MNDO-calculated optimized conformations and heats of formation are shown in Fig. 3 (a) and (b). As a result, A is the most favoured conformation, and the energy difference between A and B was calculated to be $0.942 \text{ kcal mol}^{-1}$ ($1 \text{ cal} = 4.184 \text{ J}$). This energy difference corresponds well with the stereoselectivity (ca. 80% at room temp.) in this reaction.

We thank Dr Akito Tanaka for conformational analyses by the MNDO method and Dr Toshiji Tada for the single crystal analyses.

Received, 1st October 1990; Com. 0/04411C

References

- 1 Y. Kuroda, M. Okuhara, T. Goto, M. Yamashita, E. Iguchi, M. Kohsaka, H. Aoki and H. Imanaka, *J. Antibiot.*, 1980, **33**, 259.
- 2 Y. Kuroda, M. Okuhara, T. Goto, M. Okamoto, M. Yamashita, M. Kohsaka, H. Aoki and H. Imanaka, *J. Antibiot.*, 1980, **33**, 267.
- 3 L. Chaiet, B. H. Arison, R. L. Monaghan, J. P. Spinge, J. L. Smith and S. B. Zimmerman, *J. Antibiot.*, 1984, **37**, 207.
- 4 C. R. Johnson and T. L. Marren, *Tetrahedron Lett.*, 1987, **28**, 27.
- 5 M. Fujino, S. Kobayashi, M. Obayashi, T. Fukuda, S. Shinagawa and O. Nishimura, *Chem. Pharm. Bull.*, 1974, **22**, 1857.