Pergamon

SCIENCE DIRECT®

Tetrahedron: *Asymmetry* 14 (2003) 3949–3953

TETRAHEDRON: *ASYMMETRY*

# Stereoselective synthesis of 3-amino-4-substituted-2-azetidinones via [2+2] cycloadditions of tricarbonyl($\eta^6$arene)chromium(0)complexed imines

Paola Del Buttero,[a,*] Giorgio Molteni[a] and Antonio Papagni[b]

[a]*Università degli Studi di Milano, Dipartimento di Chimica Organica e Industriale, Via Golgi 19, 20133 Milano, Italy*
[b]*Università degli Studi di Milano-Bicocca, Dipartimento di Scienze dei Materiali, Via Cozzi 53, 20125 Milano, Italy*

Received 9 September 2003; accepted 17 September 2003

**Abstract**—The stereoselective [2+2] cycloaddition reaction between the chiral tricarbonyl($\eta^6$arene) chromium(0) complexed imines **1** and **6** and phthalimidoketene affords tricarbonyl ($\eta^6$arene)chromium(0) complexed 3-phthalimido-2-azetidinones **3**, **7** and **8**, both in racemic and enantiopure form. Decomplexation and the cleavage of the phthalimido group give 3-amino-4-substituted-2-azetidinones **5** and **10**. Some insights into the stereochemical outcome of the [2+2] cycloaddition process are discussed.


## 1. Introduction

The 2-azetidinone ring represents the core of a large number of both natural and synthetic drugs employed in the treatment of different types of microbial infections.[1,2]

In this field, 3-amino-2-azetidinones are regarded as versatile intermediates since, exploiting the reactivity of amino group, they are easily transformed in a huge variety of derivatives with potential antibiotic activity.[3] Thus, different approaches have been developed in order to synthesise this nucleus in a stereo-, or better, enantioselective manner.[4] The tricarbonylchromium $\eta^6$-complexes of dissymmetrically disubstituted arene derivatives have gained an increasing popularity as effective chiral auxiliaries in a large number of stereoselective synthesis of small heterocyclic systems.[5] By exploiting them, we report herein on the first stereoselective [2+2] cycloaddition reaction between tricarbonyl($\eta^6$arene) chromium(0) complexed imines **1**, **6** and phthalimidoketenes which allows us the preparation of new 3-amino-4-substituted-2-azetidinones in both racemic and enantiopure form.

* Corresponding author. Fax: 0039-02-50314139; e-mail: paola.delbuttero@unimi.it

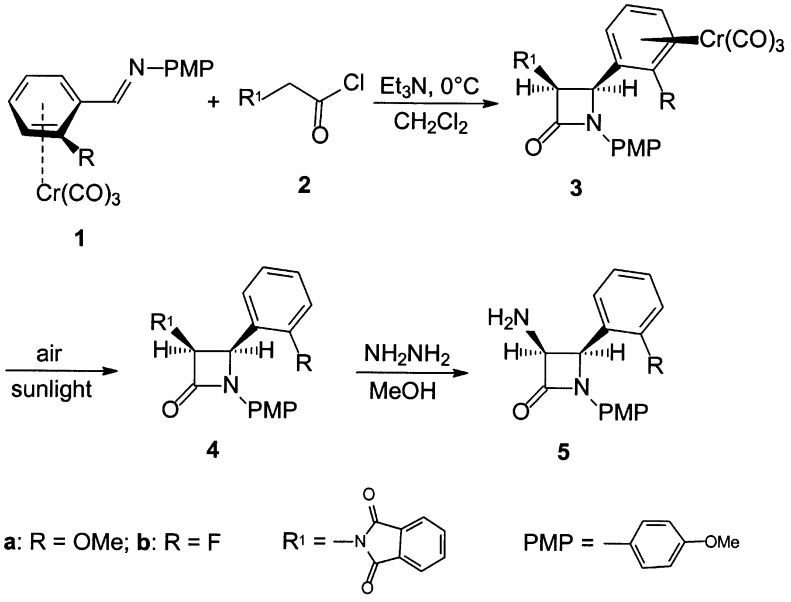
0957-4166/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2003.09.046

## 2. Results and discussion

The tricarbonyl($\eta^6$arene)chromium(0) complexed imines **1a**,**b**, dissolved in dry dichloromethane, were treated at 0°C, with a threefold excess of phthalimidoacetylchloride **2**[6] and in the presence of freshly distilled triethylamine (Scheme 1). Thus, the in situ generated phthalimidoketene reacts with the imine function under the classical Staudinger cycloaddition conditions affording 3-phthalimido-4-[tricarbonyl($\eta^6$arene)chromium(0)]complexed - 2 - azetidinones **3a** with 98% (R = OMe) and **3b** 94% (R = F) isolated yields and as single diastereoisomers. The 3,4-*cis* arrangement of the newly-formed stereocenters were deduced on the grounds of spectroscopic data. In particular, the $J_{cis}$ value of 5.4 Hz between the hydrogens in the 3- and 4-position of the 2-azetidinone ring is in perfect agreement with literature data for a *cis* geometry.[7] The exposure of dichloromethane solutions of the cycloadducts **3a**,**b** to air and sunlight oxidises the trichromiumcarbonyl moiety giving the 3-phtalimido-4-aryl-2-azetidinones **4a**,**b** in nearly quantitative yields. Among the various methods available for the cleavage of the phthalimido protecting group,[8] we found the treatment of **4** with an equimolecular amount of hydrazine in methanol solution reliable. The 3-amino-4-aryl-2-azetidinones **5a** and **5b** were obtained in 67 and 65% yields, respectively. Starting from enantiopure (1*S*)-(+)-

**1**, the enantiomeric excesses of the azetidinone derivatives **4a,b** were found to be $\geq 95\%$, as determined by $^1$H NMR in the presence of Eu(hfc)$_3$ [tris{heptafluoropropyl hydroxymethylene-(+)-camphorato} europium-(III)]. The (3*S*,4*R*) absolute configuration of the newly-formed stereocenters in the products **5a,b** has been assigned by comparing their rotation sign with that of 3-amino-1,4-diphenyl-2-azetidinone of known absolute configuration,[9] and agrees with the attack from the *si*-face of the imine function of **1**. In addition, under the accepted stereochemical model[10] of [2+2] cycloadditions between imines and ketenes, the zwitterionic intermediate **A** should be favoured[11] since unavoidable steric hindrance between the Cr(CO)$_3$ tripod and the phthalimido moiety are expected for the intermediate **B** (Fig. 1). Furthermore, the stereochemical outcome of the above [2+2] cycloaddition is in line with that previously reported by us[12] and concerning the formation of (3*S*,4*R*)-3-acetoxy-4-aryl-2-azetidinones.

When the [2+2] cycloaddition was extended to racemic tricarbonyl-[*N*-(2-methoxy cinnamylidene)-4-methoxyaniline]chromium **6**, a significant change of stereoselection was observed (Scheme 2). In fact, the cycloadducts **7** and **8** was obtained with 78% overall yield and as 22:78 diastereoisomeric mixture. The two diastereoisomers were easily separated by column chromatography, and the synthetic route leading to the racemic 3-amino-4-cinnamylidene-2-azetidinones **10** was completed through the sequential cleavage of both the tricarbonylchromium and the phthalimido pendants. Starting from enantiopure (1*S*)-(+)-**6**, the enantiomeric pure **7** and **8** have been obtained. In order to exclude any enantiomeric enrichment during any of the steps from the adduct **7** and **8**, the complete sequence to final




**Scheme 1.**

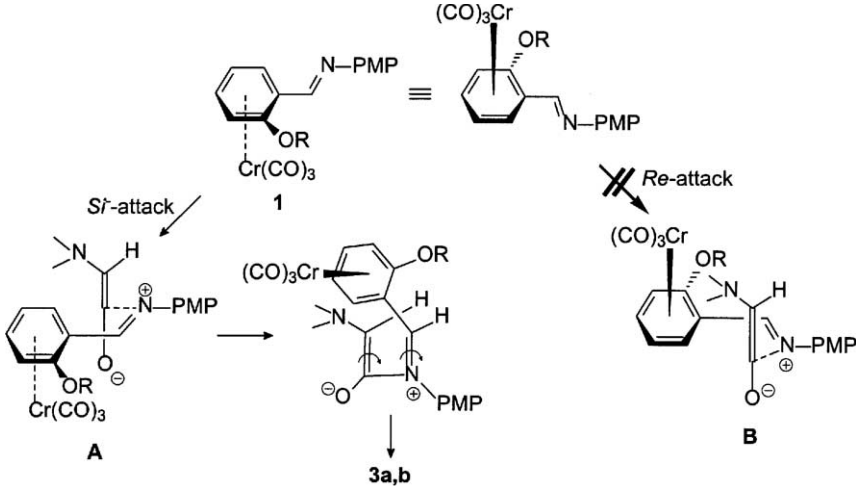
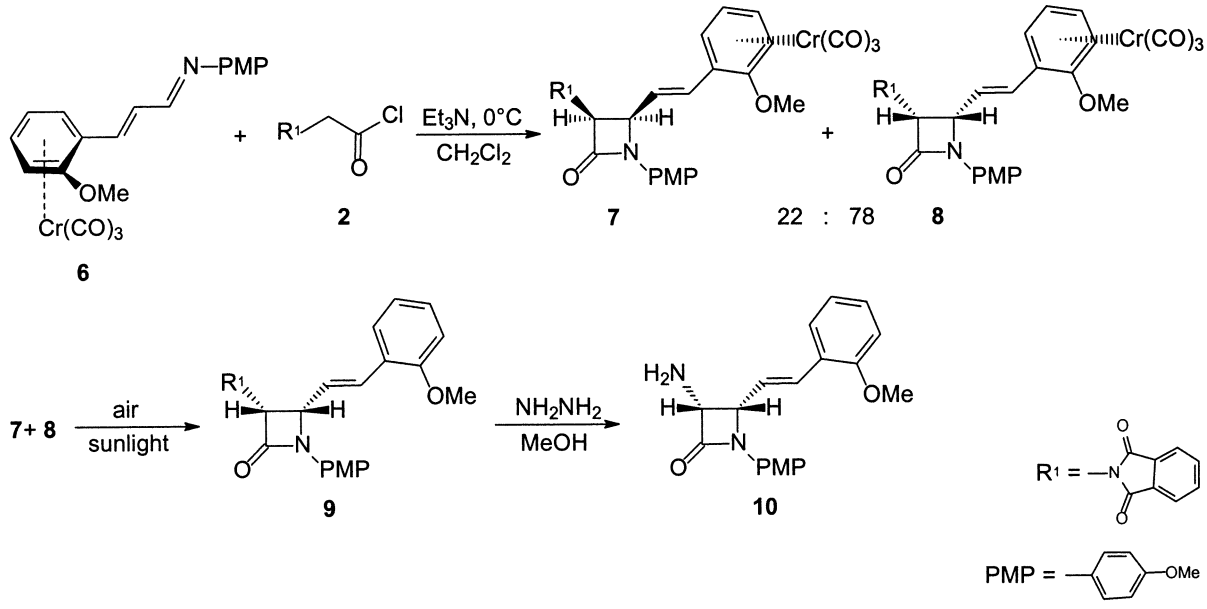



**Figure 1.**




**Scheme 2.**

3-aminoazetidinones has been performed using a mixture 22:78 of the enantiopure cycloadducts **7** and **8** (i.e. d.e. 56%). As expected, product **9** was recovered with an e.e. of 56% thus confirming that no enantiomeric enrichment has occurred during the $Cr(CO)_3$ removal. The further cleavage of the phthalimido group on **9** affords (+)-**10** $[\alpha]_D = +162$ (Scheme 2, in which the major stereoisomer is shown). Although surprisingly, the stereoselectivity pattern of the initial [2+2] cycloaddition is paralleled from that reported in the similar reaction between (1*S*)-(+)-**6** and acetoxyketene, which gave the (3*R*,4*S*)-3-acetoxy-4-cinnamylidene-2-azetidinone as the major stereoisomer, as it was shown on the basis of CD curves. Therefore, it appears reasonable that the newly-formed stereocentres in the 2-azetidinones **3** and the major stereoisomer **8** are reversed. On these basis, in analogy with the literature value of (−)-(3*S*,4*R*)-1-benzyl-3-amino-4-cinnamylidene-2-azetidinone,[9] we have assigned the (3*R*,4*S*) configurations also to the (+)-**10** derivative.

The depicted results are consistent with the mechanism outlined in Figure 2. First, it is reasonable that the *s-cis* and the *s-trans* conformers of **6** are in equilibrium and as consequence of this, an attack onto the re-face of imine function in the *s-cis* conformer of **6** is possible. According to the above-mentioned stereochemical model,[10] this possibility produces the two concurrent zwitterionic intermediates **C** and **D**. As highlighted in Figure 2, the negative charged oxygen is closer to the electron-withdrawing $Cr(CO)_3$ tripod (chromium carbonyls in many instances show a Lewis acid behaviour) in the intermediate **D** than in **C**. Thus, a higher stabilising electrostatic interaction should be expected in **D** when compared to **C**. To substantiate the latter sen-

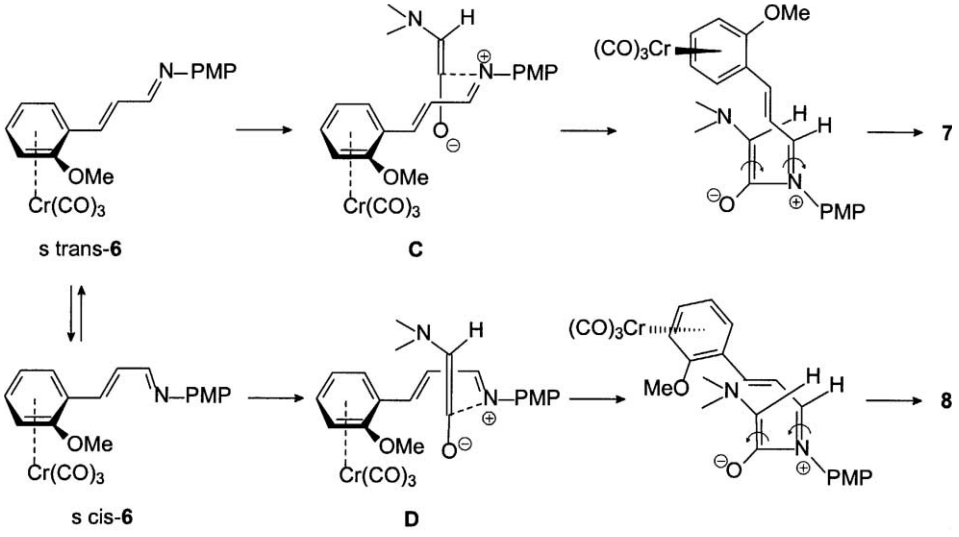



**Figure 2.**

tence, we optimised the ground state geometry of both *s-trans*- and *s-cis*-**6** at the PM3[13] semiempirical level.[14] Next, we estimated the distances between $O^-$ and the $Cr(CO)_3$ fragments in both the intermediates **C** and **D** through the data provided by Cossio et al.[15] These distances were 4.3 Å for **C** and 3.2 Å for **D**, and considering the fact that electrostatic interactions (or electrostatic energies) are inversely proportional to the distances between charges, the intermediate **D** should be slightly more stabilised over **C**. This extra stabilisation could account for the observed diastereoselectivities.

## 3. Conclusions

Enantiopure chromium(0) complexed benzylidene imines **1** allow the corresponding 3-amino 2-azetidinones **3a**,**b** to be obtained in good yield and in 98% e.e. As expected, a decrease in the diastereoselectively was observed using enantiomerically pure chromium complexed cinnamylidene imines **6**. From the described results it comes that combining the known stereochemical rules for the behaviour of [2+2] cycloadditions and chiral tricarbonylchromium arenes, the attack of the imine onto the phthalimidoketene take place exclusively from the *Si*-face of (+)-(1*S*)-**1** and mainly from the *Re*-face for the (+)-(1*S*)-**6**. Therefore, on the basis of the absolute configuration of the starting imine it is possible to predict the absolute configuration of new stereocentres in the final products.

## 4. Experimental

Melting points were determined with a Büchi apparatus in open tubes and are uncorrected. IR spectra were recorded with a Perkin–Elmer 1725 X spectrophotometer. Mass spectra were determined with a VG-70EQ apparatus. $^1$H NMR (300 MHz), $^{13}$C and $^{19}$F NMR (75 MHz) spectra were taken with a Bruker AC 300 or a Bruker AMX 300 instrument (in $CDCl_3$ solutions at room temperature). Chemical shifts are given as ppm from tetramethylsilane and *J* values are given in Hz. Optical rotations were recorded on a Perkin–Elmer 241 Polarimeter at the sodium D line.

### 4.1. [2+2] Cycloaddition between phthalimidoketene and tricarbonylchromium complexed imines 1a,b and 6. General procedure

A solution of **2** (0.80 g, 3.6 mmol) in dry dichloromethane (15 mL) was added dropwise to a solution of the appropriate tricarbonylchromium complexed imine **1a**,**b** or **6** (0.6 mmol) and triethylamine (0.67 mL, 4.8 mmol) in dry dichloromethane (6 mL) at 0°C. The reaction mixture was then warmed at room temperature and monitored by TLC (diethyl ether). After about 1 h the mixture was quenched with brine, extracted with dichloromethane (2×20 mL).

When starting from **1a**,**b**, evaporation of the solvent gave solid which was crystallised from ethanol giving **3a**,**b**.

When starting from **6**, evaporation of the solvent gave a residue which was chromatographed on a silica gel column with diethylether:ethyl acetate 9:1 giving **7** and **8**.

Compound **3a**: (0.33 g, 98%); mp 125°C (with decomposition); IR: (Nujol) 1975, 1890, 1765, 1730 ($cm^{-1}$); $^1$H NMR $\delta$ 3.60 (s, 3H), 3.80 (s, 3H), 4.70 (d, *J* 6.5 Hz, 1H), 4.8 (t, *J* 6.2 Hz, 1H), 5.30 (t, *J*=6.5 Hz, 1H), 5.60 (d, *J* 5.6 Hz, 1H), 5.70 (d, *J* 6.2 Hz, 1H), 5.80 (d, *J* 5.6 Hz, 1H), 6.9 (AB system, 2H), 7.6 (AB system, 2H), 7.6–7.8 (m, 4H); MS: *m*/*z* 564 ($M^+$). Anal. calcd for $C_{28}H_{20}CrN_2O_8$ C, 59.58; H, 3.57; N, 4.96. Found: C, 59.56; H, 3.58; N, 4.95.

Compound (3*S*,4*R*)-**3a**: $[\alpha]_D^{25}=-238.0$ ($CHCl_3$, *c* 0.068) [from enantiopure (1*S*)-(+)-**1a**].

Compound **3b**: (0.31 g, 94%); mp 198°C (with decomposition); IR: (Nujol) 1970 1905, 1865, 1760, 1725 ($cm^{-1}$); $^1$H NMR $\delta$ 3.80 (s, 3H), 4.07 (dt, *J* 6.2, 2.0 Hz, 1H), 5.10 (t, *J* 5.7 Hz, 1H), 5.30 (dt, *J* 6.5, 2.8 Hz, 1H), 5.55–5.65 (m, 2H), 5.8 (d, *J* 5.5 Hz, 1H), 7.00 (AB system, 2H), 7.70 (AB system, 2H), 7.7–7.9 (m, 4H). $^{19}$F NMR $\delta$ –141.65; MS: *m*/*z* 552 ($M^+$). Anal. calcd for $C_{27}H_{17}CrN_2O_7F$ C, 58.70; H, 3.10; N, 5.07. Found: C, 58.68; H, 3.11; N, 5.07.

Compound (3*S*,4*R*)-**3b**: $[\alpha]_D^{25}=-25.5$ ($CHCl_3$, *c* 0.11) [from enantiopure (1*S*)-(+)-**1b**].

Compound **7**: (60 mg, 17%); mp 175°C (from ethanol); IR: (Nujol) 1975, 1895, 1760, 1730 ($cm^{-1}$); $^1$H NMR ($CDCl_3$) $\delta$ 3.70 (s, 3H), 3.75 (s, 3H), 4.85 (t, *J* 6.3 Hz, 1H), 4.95 (dd, *J* 5.4, 8.6 Hz, 1H), 4.99 (d, *J* 6.3 Hz, 1H), 5.45 (t, *J* 6.3 Hz, 1H), 5.65 (d, *J* 6.3 Hz, 1H), 5.85 (d, *J* 5.4 Hz, 1H), 6.3 (dd, *J* 8.6, 16.1 Hz, 1H), 6.9 (d, *J* 16.1 Hz, 1H), 7.4–8 (m, 8H); MS: *m*/*z* 590 ($M^+$). Anal. calcd for $C_{30}H_{22}CrN_2O_8$ C, 61.02; H, 3.76; N, 4.46. Found: C, 61.04; H, 3.77; N, 4.45.

Compound (3*S*,4*R*)-**7**: $[\alpha]_D^{25}=+337.9$ ($CHCl_3$, *c* 0.015) [from enantiopure (1*S*)-(+)-**6**].

Compound **8**: (0.22 g, 61%); mp 185°C (from ethanol). IR: (Nujol) 1970, 1890, 1770, 1730 ($cm^{-1}$); $^1$H NMR $\delta$ 3.70 (s, 3H), 3.75 (s, 3H), 4.81 (t, *J* 6.8 Hz, 1H), 5.0 (dd, *J* 8.7, 5.5 Hz, 1H), 5.2 (d, *J* 6.8 Hz, 1H), 5.4 (t, *J* 6.4 Hz, 1H), 5.6 (d, *J* 6.4 Hz, 1H), 5.7 (d, *J* 5.6 Hz, 1H), 6.28 (dd, *J* 8.7, 16.1 Hz, 1H), 7.1 (d, *J* 16.1 Hz, 1H), 6.8–7.8 (m, 8H); MS: *m*/*z* 590 ($M^+$). Anal. calcd for $C_{30}H_{22}CrN_2O_8$ (590.5) C, 61.02; H, 3.76; N, 4.46. Found: C, 61.06; H, 3.75; N, 4.46.

Compound (3*R*,4*S*)-**8**: $[\alpha]_D^{25}=+646.6$ ($CHCl_3$, *c* 0.025) [from enantiopure (1*S*)-(+)-**6**].

### 4.2. Decomplexation of 3a,b and 7+8

A solution of **3a**,**b**, or **7**+**8** (0.4 mmol) in dichloromethane (15 mL) was exposed to air and sunlight for 6 h. The solvent was removed under reduced pressure, the residue was taken up with diethylether

and filtered over a pad of Celite. The organic layer was evaporated under reduced pressure and the residue was crystallised by ethanol giving **4a**,**b** or **9**.

Compound **4a**: (0.16 g, 95%); mp 208°C (from ethanol); IR: (Nujol) 1800, 1760, 1720 ($cm^{-1}$); $^1H$ NMR $\delta$ 3.60 (s, 3H), 3.80 (s, 3H), 5.60 (d, $J$ 5.44 Hz, 1H), 5.80 (d, $J$ 5.44 Hz, 1H), 6.6–7.6 (m, 12H); MS: $m/z$ 428 ($M^+$). Anal. calcd for $C_{25}H_{20}N_2O_5$ C, 70.08; H, 4.71; N, 6.54. Found: C, 70.10; H, 4.70; N, 6.55.

Compound (3*S*,4*R*)-**4a**: $[\alpha]_D = -31.0$ ($CHCl_3$ $c$ 0.025).

Compound **4b**: (0.17 g, 97%); mp 198°C (from ethanol); IR: (Nujol) 1785, 1758, 1727 ($cm^{-1}$); $^1H$ NMR $\delta$ 3.80 (s, 3H); 5.70 (d, $J$ 5.5 Hz, 1H); 5.80 (d, $J$ 5.5 Hz, 1H); 6.90 (AB system, 2H); 7.70 (m, 4H); MS: $m/z$ 416 ($M^+$). Anal. calcd for $C_{24}H_{17}N_2O_4F$ C, 69.23; H, 4.12; N, 6.73. Found: C, 69.20; H, 4.11; N, 6.70.

Compound (3*S*,4*R*)-**4b**: $[\alpha]_D = -4.8$ ($CHCl_3$, $c$ 0.25).

Compounds **9**: (0.18 g, 86%); IR: (Nujol) 1785, 1750, 1710 ($cm^{-1}$); $^1H$ NMR $\delta$ 3.78 (s, 1H), 3.80 (s, 3H), 5.10 (dd, $J$ 5.5, 16.19 Hz, 1H), 5.68 (d, $J$ 5.5 Hz, 1H), 5.68 (dd, $J = 8.9$, 16.2 Hz, 1H); 7.10 (d, $J$ 16.2 Hz, 1H); 6.8–7.7 (m, 12H); MS: $m/z$ 454 ($M^+$). Anal. calcd for $C_{27}H_{22}N_2O_5$ C, 71.35; H, 4.88; N, 6.16. Found: C, 71.33; H, 4.85; N, 6.74. e.e. $\geq 98\%$ by $^1H$ NMR ($Eu(hfc)_3$. $[\alpha]_D^{25} = +578.6$ ($CHCl_3$, $c$ 0.02 $CHCl_3$)

### 4.3. Cleavage of the phthalimido group. General procedure

To a suspension of **4a**,**b** or **9** (0.6 mmol) and hydrazine dihydrochloride (0.83 g, 2.7 mmol) in dry methanol (8.0 mL), a solution of triethylamine (0.7 mL, 5.4 mmol) in dry methanol (1.0 mL) was added dropwise. The mixture was heated at 40°C for 4 h and then cooled, added with water (30 mL) and extracted with ethyl acetate. The solvent was evaporated and the residue was chromatographed on a silica gel column with dichloromethane: ethyl acetate 1:1 giving **5a**,**b** or **10**.

Compound **5a**: (0.12 g, 67%); mp 209°C (from dichloromethane/ethyl acetate 1:1); IR: (Nujol) 3400, 3350, 1740 ($cm^{-1}$); $^1H$ NMR $\delta$ 1.60 (br s, 2H), 3.70 (s, 3H), 3.85 (s, 3H), 4.60 (d, $J$ 5.4 Hz, 1H), 5.50 (d, $J = 5.4$ Hz, 1H), 6.8-7.1 (m, 8H); MS: $m/z$ 298 ($M^+$). Anal. calcd for $C_{17}H_{18}N_2O_3$ C, 68.44; H, 6.08; N, 9.39. Found: C, 68.34; H, 6.07; N, 9.36.

Compound (3*S*,4*R*)-**5a**: $[\alpha]_D = -80.0$ ($CHCl_3$, $c$ 0.10) [from (3*S*,4*R*)-**4a**].

Compound **5b**: (0.14 g, 81%); mp 120°C (from dichloromethane/ethyl acetate 1:1); IR: (Nujol) 3390, 3310, 1745 ($cm^{-1}$); $^1H$ NMR $\delta$ 1.60 (br s, 2H), 3.80 (s, 3H), 4.70 (d, $J$ 5.4 Hz, 1H), 5.50 (d, $J$ 5.4 Hz, 1H), 6.8–7.3 (m, 8H); MS: $m/z$ 286 ($M^+$). Anal. calcd for $C_{16}H_{15}N_2O_2F$ C, 67.12; H, 5.28; N, 9.78. Found: C, 67.20; H, 5.26; N, 9.76.

Compound (3*S*,4*R*)-**5b**: $[\alpha]_D = -144.2$ ($CHCl_3$, $c$ 0.57) [from (3*S*,4*R*)-**4b**].

Compounds **10**: (0.09 g, 45%); undistillable yellow oil; IR: (Nujol) 3385, 3315, 1750 ($cm^{-1}$); $^1H$ NMR $\delta$ 1.70 (s, 2H), 3.75 (s, 3H), 3.82 (s, 3H), 4.50 (dd, $J$ 4.7, 5.5 Hz, 1H), 4.80 (dd, $J$ 7.6, 5.5 Hz, 1H), 6.26 (dd, $J$ 7.6, 16.1 Hz, 1H), 7.11 (d, $J$ 16.1 Hz, 1H), 6.8–7.5 (m, 8H); MS: $m/z$ 324 ($M^+$). Anal. calcd for $C_{19}H_{20}N_2O_3$ C, 70.35; H, 6.21; N, 8.64. Found: C, 70.40; H, 6.20; N, 8.65.

Compound (3*S*,4*R*)-**10**: $[\alpha]_D = +162$ ($CHCl_3$, $c$ 0.2 $CHCl_3$).

## Acknowledgements

Thanks are due to MURST and CNR for financial support.

## References

1. Samarendra, C. I.; Maiti, N.; Micetich, R.; Daneshtalab, M.; Atchison, K.; Phillips, O. A.; Kunugita, C. *J. Antibiot*. **1994**, *47*, 1030.
2. (a) *Chemistry and Biology of β-Lactam Antibiotics* Morris, R. B.; Gorman, M., Eds.; Academic Press: New York, 1982; (b) Niccolai, D.; Tarsi, L.; Thomas, R. J. *Chem. Commun*. **1997**, 2333.
3. Sammes, P. G. *Chem. Rev*. **1976**, *76*, 113.
4. *The Organic Chemistry of β-Lactams*; Georg, G. I., Ed.; VCH Press: New York, 1993.
5. Davies, S. G.; McCarthy, T. D. In *Comprehensive Organometallic Chemistry II*; Abel, E. W.; Stone, F. G.; Wilkinson, G., Eds.; Pergamon Press: Oxford, 1995; Vol. 12.
6. Sheenan, J. C.; Ryan, J. J. *J. Am. Chem. Soc*. **1951**, *73*, 1204.
7. (a) Prasad, J. S.; Liebeskind, L. S. *Tetrahedron Lett*. **1988**, *29*, 4253; (b) Palomo, C.; Arrieta, A.; Cossio, F. P.; Aizpurna, J. M.; Mielgo, A.; Aurrekoetxea, N. *Tetrahedron Lett*. **1990**, *31*, 6429.
8. (a) Osby, J. O.; Martin, M. G.; Ganem, B. *Tetrahedron Lett*. **1984**, *25*, 2093; (b) Kambya, T.; Hashimoto, M.; Nakaguchi, O.; Oku, T. *Tetrahedron* **1978**, *35*, 323.
9. Ikota, N. *Chem. Pharm. Bull*. **1990**, *38*, 1601.
10. Hegedus, L. S.; Montgomery, J.; Narukawa, Y.; Snustad, D. C. *J. Am. Chem. Soc*. **1991**, *113*, 5784.
11. Solladiè-Cavallo, A. In *Advances in Metal-Organic Chemistry*; Liebeskind, L. S., Ed.; JAI Press: Greenwich, 1989; Vol. 1, p. 99.
12. Baldoli, C.; Del Buttero, P.; Licandro, E.; Maiorana, S.; Papagni, A. *Tetrahedron: Asymmetry* **1994**, *5*, 809.
13. Stewart, J. J. P. *J. Comput. Chem*. **1989**, *10*, 209 and 221.
14. As implemented in the Hyper Chem Release 6.01 version for Windows; Hypercube Inc., 2000.
15. Cossío, F. P.; Arrieta, A.; Lecea, B.; Ulgade, J. M. *J. Am. Chem. Soc*. **1994**, *116*, 2085.