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DIASTEREOSELECTIVE SYNTHESIS OF SPIRO-β-LACTAMS *VIA* STAUDINGER REACTION

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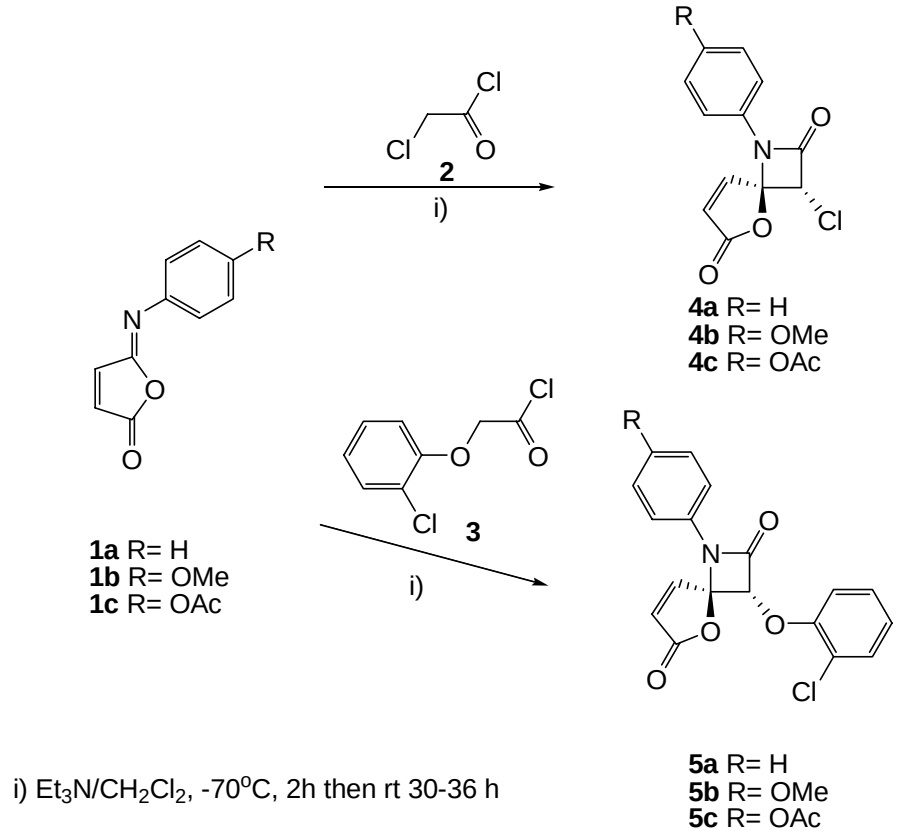
Abstract - In this work, eleven new spiro-β-lactams have been prepared using the Staudinger reaction of isomaleimides (**1a-d**) and carboxylic acids (chloroacetic acid, (-)-menthoxyacetic acid (**7**) and an oxazolidinone derived acid (**10**)) in the presence of triphosgene under mild condition. All reactions have been shown to be stereoselective. The new stereogenic centers were assigned by X-ray diffraction.

INTRODUCTION

The stereoselective synthesis of β-lactams has received considerable attention in recent years. In particular, the asymmetric Staudinger reaction between a ketene and an imine has been extensively studied[1] due to the renewed and growing interest in β-lactams.[2] These heterocycles are very useful entities in organic chemistry with interesting biological activity. For example, the recent discovery of their use as cholesterol absorption inhibitors,[3] thrombin inhibitors[4] and anti-hyperglycemic agents[5] maintains the interest of the chemical community in these compounds. Aditionally, spiro-β-lactams can act as antiviral,[6] and antibacterial agents,[7] and also inhibit cholesterol absorption.[8] In a previous paper we have reported the synthesis of spiro-β-lactams derived from isomaleimides[9] (**1a-c**) with two acid chlorides (**2** or **3**) by means of the Staudinger reaction. (Scheme 1)

Herein, we report the synthesis of eleven new spiro-β-lactams [**4d**, (3*R*,4*R*,1'*R*,2'*S*,5'*R*)-**8b**, (3*S*,4*S*,1'*R*,2'*S*,5'*R*)-**8b**, (3*R*,4*R*,1'*R*,2'*S*,5'*R*)-**8c**, (3*S*,4*S*,1'*R*,2'*S*,5'*R*)-**8c**, (3*R*,4*R*,4'*R*)-**11a**, (3*S*,4*S*,4'*R*)-**11a**, (3*R*,4*R*,4'*R*)-**11b,** (3*S*,4*S*,4'*R*)-**11b,** (3*R*,4*R*,4'*R*)-**11d** and (3*S*,4*S*,4'*R*)-**11d**] using the Staudinger reaction. These spiro-β-lactams are obtained from the reaction of isomaleimides (**1a-d**) with chloroacetic acid (**6**), (-)-menthoxyacetic acid (**7**) and (*R*)-(4-phenyloxazolidin-2-one-3-yl)acetic acid (**10**).

Furthermore, the use of triphosgene under mild conditions leading to the construction of β-lactams is described.



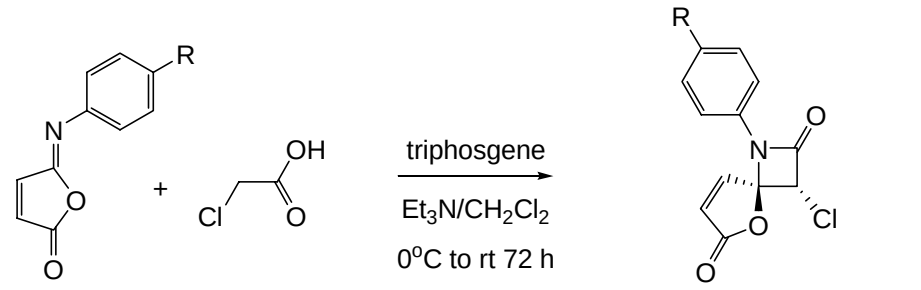
Scheme 1

RESULTS AND DISCUSSION

The isomaleimides (**1a-d**) were allowed to react with chloroacetic acid in the presence of triphosgene and triethylamine to give stereoselective the spiro-β-lactams (**4a, 4b** and **4d**) in 40-76% yields (Scheme 2). In all these cases the yields were higher than those using acid chlorides.[9]

The NMR data for spiro-β-lactams (**4a** and **4b**) were in agreement with those previously described.[9] The structure of spiro-β-lactam (**4d**) was established by ^{1}H and ^{13}C NMR spectroscopy. Accordingly, the ^{1}H NMR spectrum of **4d** showed a singlet at 5.31 ppm corresponding to H-3 of the β-lactam ring whereas the signals of the vinylic protons having a coupling constant of 5.7 Hz were observed at 7.55 and 6.56 ppm. The ^{13}C NMR spectrum of **4b** showed two carbonyl signals at 167.6 (C-6) and 157.7 ppm (C-2); the signal at 94.4 ppm was assigned to C-4 and that at 64.7 ppm was assigned to C-3, on the basis of proton-carbon correlation 2D spectra. Furthermore, the relative configuration at C-3 and C-4 for **4d** was established by X-ray crystallography, which confirmed the structure of this compound (Figure 1).[11]

In all the cases studied, the reactions were found to be stereoselective and only β-lactams in which the heteroatoms at C-4 and C-3 in the β-lactam ring are in a relative *anti* relationship were formed (Scheme 2).



1a R= H
1b R= OMe
1d R= Me

6

4a R= H (66 %)
4b R= OMe (76%)
4d R= Me (40 %)

Scheme 2

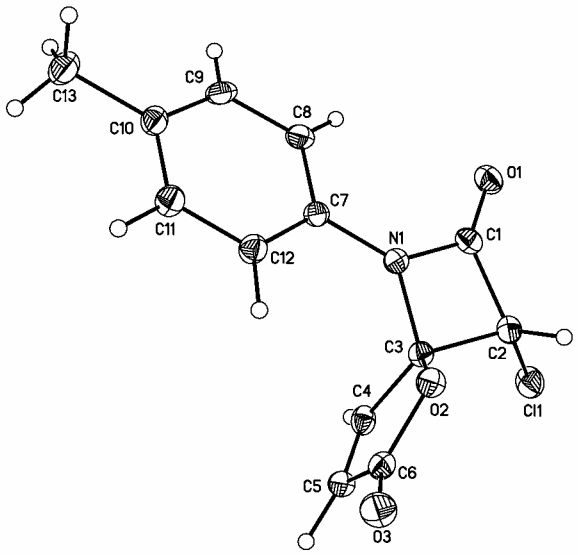
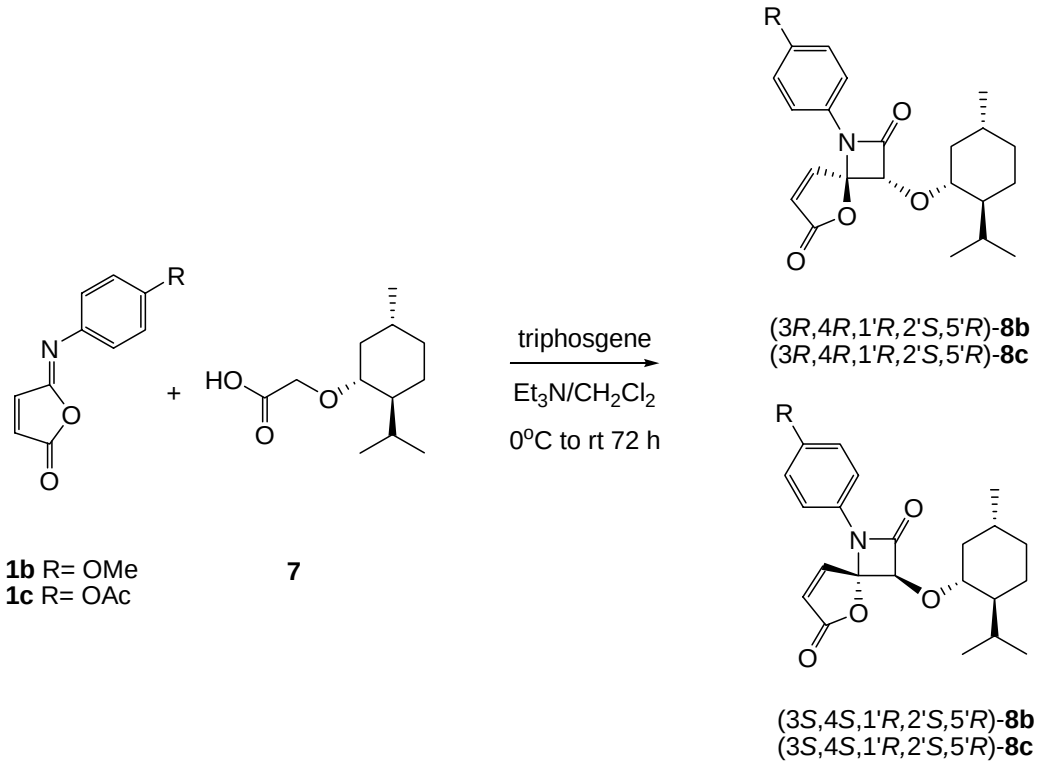


Figure 1 X-Ray structure of compound **4d**

The triphosgene was also successfully employed in the synthesis of spiro-β-lactams derived from isomaleimides (**1**) and chiral acids derived from (-)-menthol (**7**) [10] or from oxazolidinone (**10**). The reaction of the ketene derived from (-)-menthoxyacetic acid (**7**) with isomaleimides (**1b** and **1c**) in the presence of triethylamine and triphosgene, gave a diastereomeric mixture (1:1) of spiro-β-lactams (3*R*,4*R*,1'*R*,2'*S*, 5'*R*)-(**8**) and (3*S*,4*S*,1'*R*,2'*S*,5'*R*)-(**8**) (Scheme 3). The ratio of these two diastereomers was determined by ^{1}H NMR. Our attempts to separate these diastereomers by TLC, column chromatography, or by fractional crystallization were unsuccessful. Thus, these compounds were characterized by the spectroscopic data obtained on the diastereomeric mixtures.

The diastereomers (3*S*,4*S*,1'*R*,2'*S*,5'*R*)-**8b** and (3*R*,4*R*,1'*R*,2'*S*,5'*R*)-**8b** co-crystallized and the absolute configuration of the diastereomeric mixture was established from single crystal X-ray analysis (Figure 2).



Scheme 3

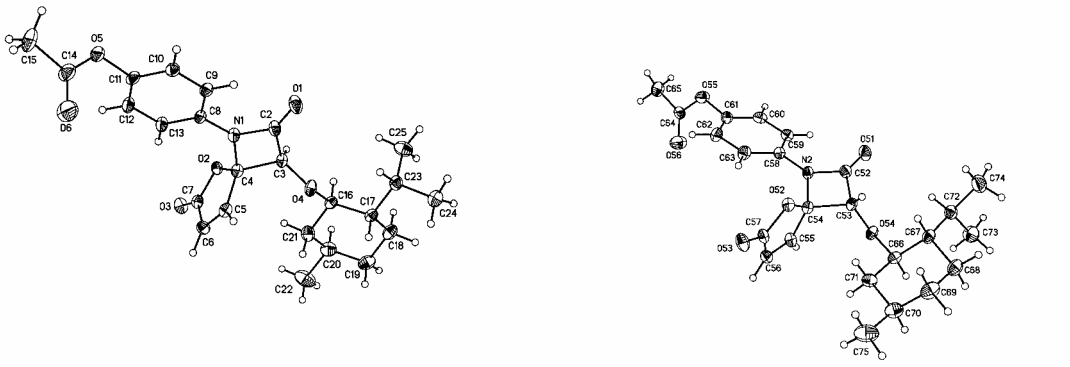


Figure 2a X-Ray structure of compounds (3*S*,4*S*,1'*R*,2'*S*,5'*R*)-(**8b**) and (3*R*,4*R*,1'*R*,2'*S*,5'*R*)-(**8b**)

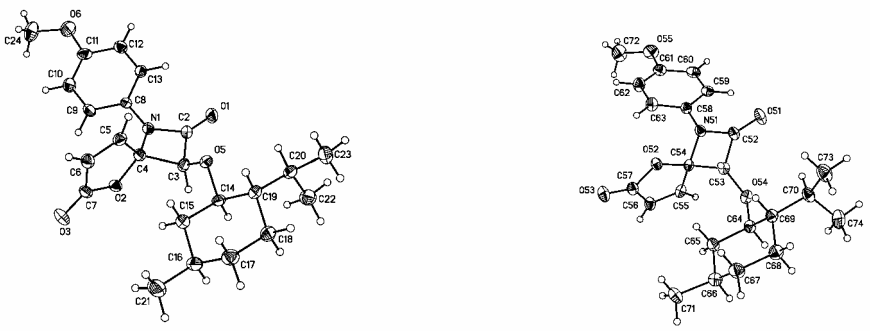


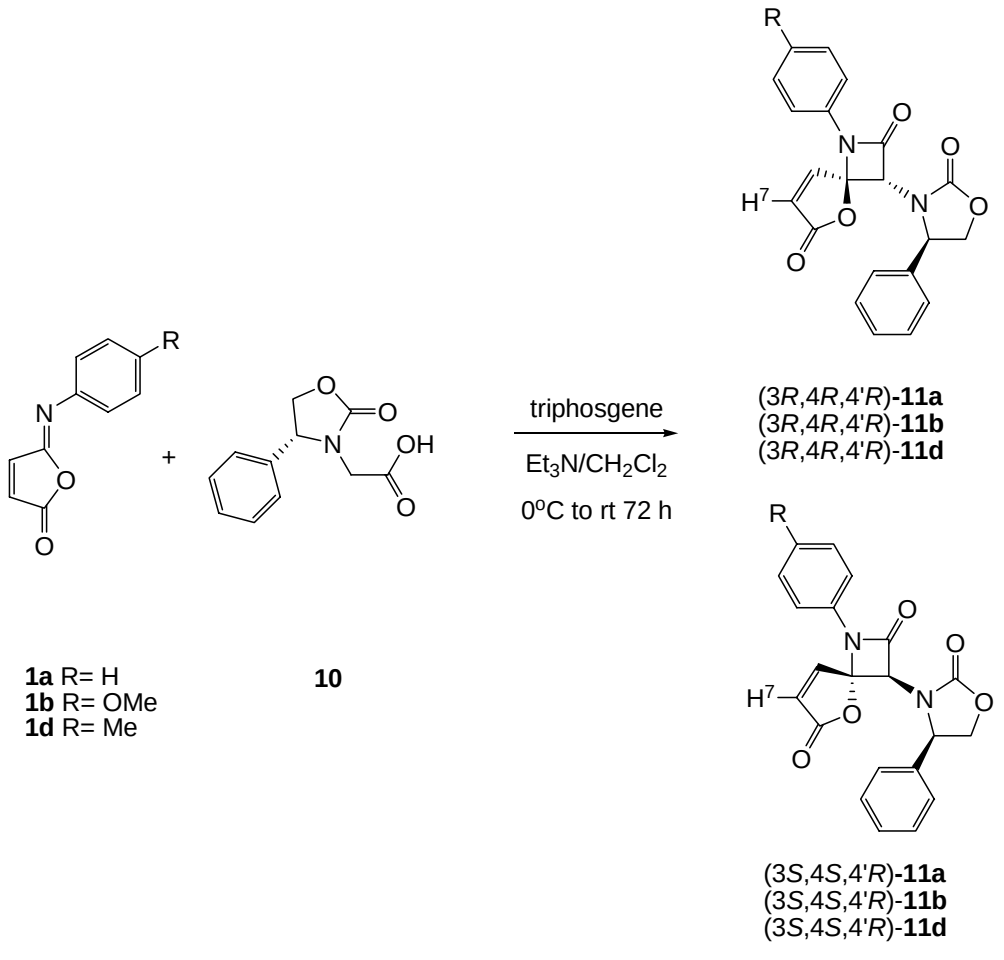
Figure 2b X-Ray structure of compounds (3*S*,4*S*,1'*R*,2'*S*,5'*R*)-(**8c**) and (3*R*,4*R*,1'*R*,2'*S*,5'*R*)-(**8c**)

Isomaleimides **1a**,**1b** and **1d** were also allowed to react with the oxazolidinone derived acid (**10**) in the presence of triphosgene and triethylamine to give diastereomeric mixtures of the spiro-β-lactams (3*R*,4*R*,4'*R*)-(**11a, b, d**) and (3*S*,4*S*,4'*R*)-(**11a, b, d**) (Scheme 4) in moderate yields (see Table 3). The ratio of the two diastereomers was determined by ^{1}H NMR spectral data on the crude reaction products (Table 3). Again, our attempts to separate these diastereomers by column chromatography were unsuccessful. However, in all cases, the diastereomers (**11**) were isolated in pure form by fractional crystallization.

Table 3 Diastereoselectivity and chemical yields of **11**

Entry	R	*ds*[a] (3*R*,4*R*,4'*R*)-**11** : (3*S*,4*S*,4'*R*)-**11**	Yield (%)[b]
1	H	3:2	51
2	Me	2:1	58
3	OMe	3:2	90

a) Determined by integration of the ^{1}H NMR signals in the crude reaction mixture.
b) Refers to the mixture of pure diastereomers, after isolation.



Scheme 4

The structures of spiro-β-lactams (**11a**, **11b** and **11d**) were established by ^{1}H and ^{13}C NMR spectroscopy. The signal of H-7 of the compounds with the (3*S*,4*S*,4'*R*) configuration is shifted to lower frequencies compared to those compounds with the (3*R*,4*R*,4'*R*) configuration. These differences of δ are due to the aromatic ring on the oxazolidinone which is located in the vicinity of H-7 only in the (3*S*,4*S*,4'*R*) diastereomers.

The absolute configuration of the spiro β-lactams (3*R*,4*R*,4'*R*)-(**11a**) and (3*S*,4*S*,4'*R*)-(**11b**) was established from single crystal X-ray analysis.[11] The configuration of the spiro β-lactam (**11a**) was assigned as 3(*R*), and 4(*R*) on the basis of the known absolute (4'*R*) configuration of the (4-phenyloxazolidin-2-one-3-yl)acetic acid (**10**) (Figure 3). The configuration of the spiro β-lactam **11b** was assigned as 3(*S*), and 4(*S*) on the basis of the known absolute (4'*R*) configuration of the phenyloxazolidinone moiety (Figure 4).

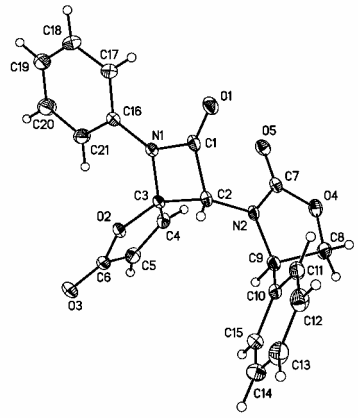


Figure 3 X-Ray structure of compound (3*R*,4*R*,4'*R*)-(**11a**)

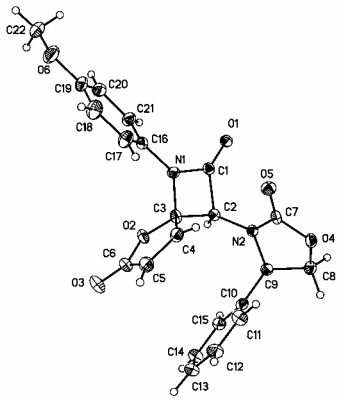
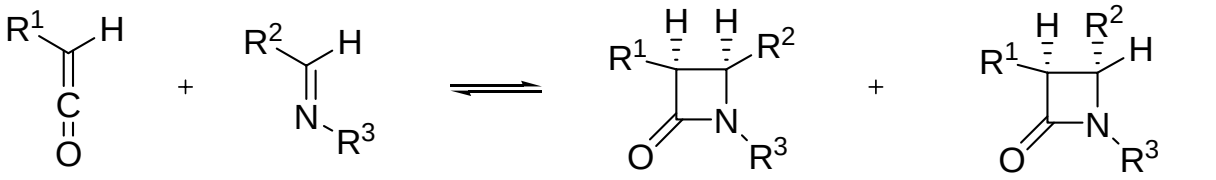


Figure 4 X-Ray structure of compound (3*S*,4*S*,4'*R*)-(**11b**)

Reaction mechanism

Previous studies[12,13] on the Staudinger reaction have shown it involves the intermediacy of zwitterionic intermediates rather than being a direct [2+2] cycloaddition between ketenes and imines. Accordingly, Xu[13] has suggested that the ring closure step should be viewed as an intramolecular nucleophilic addition of an enolate to the imine moiety. In the case of the Staudinger reaction between ketenes and imidates (R^2 = OR) only *trans* β-lactams are always obtained, regardless of the nature of the remaining constituents (Scheme 5).



***cis*-β-lactam** ***trans*-β-lactam**

Scheme 5

Until now, we have not been able to find a definitive explanation about the differences in diastereoselectivity in these reactions and a number of interesting questions raised are still being addressed in our laboratory. Further studies towards the application of this process in the synthesis of modified β-amino acids and β-peptides are ongoing and the results will be discussed in due time.

CONCLUSIONS

We have developed a simple method for the synthesis of spiro-β-lactams. We also demonstrated that the standard Staudinger ketene-isomaleimide cycloaddition can be efficiently used to prepare spiro β-lactams. This strategy is quite general, allowing the use of different ketene derivatives as starting materials.

EXPERIMENTAL

Flasks, stirring bars, and needles used were oven-dried for ca. 12 h at 120 ^{o}C and allowed to cool under a nitrogen atmosphere. Anhydrous CH_2Cl_2 was obtained by distillation from CaH_2. TLC was performed on Merck-DC-F_{254} plates and detection was made by shining 254 nm UV light. Column chromatography was performed using Merck silica gel (70-230 mesh). All melting points were recorded on a Büchi Melting Point B-540 and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a JEOL Eclipse+400 spectrometer at 400 and 100 MHz, respectively. Chemical shifts (δ) are indicated in ppm downfield from internal TMS reference; the coupling constants (*J*) are given in Hz. IR (cm^{-1}) absorption spectra were recorded on a Perkin-Elmer FT-IR Spectrum GX spectrometer. Optical rotations were measured on a Perkin-Elmer Model 341 Polarimeter, using the sodium D-line (586 nm). Elemental analyses were performed on a Perkin-Elmer Serie II CHNS/O Analyzer 2400.

General procedure for the synthesis of spiro-β-lactams.

A solution of triphosgene (1 mmol) in anhydrous CH_2Cl_2 (10 mL) was added slowly to a solution of acid (1 mmol), isomaleimide (1 mmol) and Et_3N (3 mmol) in anhydrous CH_2Cl_2, (15 mL) at 0 ^{o}C. The reaction mixture was then allowed to warm up to rt and stirred further for 72 h. The reaction mixture was

then washed with water (20 mL) and a saturated aqueous $NaHCO_3$ (10 mL). The organic layer was dried over anhydrous magnesium sulphate and the solvent was removed in vacuo to get the crude product, which was purified by column chromatography on silica gel (70-230 mesh) eluting with hexane-EtOAc (9:1) to give pure β-lactams.

3-Chloro-1-phenyl-5-oxa-1-azaspiro[3.4]oct-7'-ene-2,6-dione (4a)

The general procedure using *N*-phenylisomaleimide (**1a**) and chloroacetic acid was followed to obtain 66% yield of **4a** as a white solid. All spectroscopic and physical data were in complete agreement with those published. mp 132-133 ºC, Lit.,[9] mp 132-133 °C.

3-Chloro-1-*p*-methoxyphenyl-5-oxa-1-azaspiro[3.4]oct-7'-ene-2,6-dione (4b)

The general procedure using *N*-p-methoxyphenylisomaleimide (**1b**) and chloroacetic acid was followed to give 76% yield of **4b** as a white solid mp 128-130 ºC. All spectroscopic and physical data were in complete agreement with that published. Lit.,[9] mp128-130 °C.

3-Chloro-1-*p*-methylphenyl-5-oxa-1-azaspiro[3.4]oct-7'-ene-2,6-dione (4d)

The general procedure using *N*-*p*-methylphenylisomaleimide (**1d**) and chloroacetic acid was followed to give 40% yield of **4d** as a white solid; mp 146-148 °C. ^{1}H NMR ($CDCl_3$): δ 7.55 (d, J = 5.6 Hz, 1H, H-8); 7.16 (d, J = 8.4 Hz, 2H, H-2′, H-6′); 7.11 (d, J = 8.4 Hz, 2H, H-3′, H-5′); 6.56 (d, J = 5.6 Hz, 1H, H-7); 5.31 (s, 1H, H-3).2.30 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$): δ 167.6 (C-6), 157.7 (C-2), 149.9 (C-8), 136.9 (C-4′), 132.2 (C-1′), 130.1 (C-2′, C-6′), 127.8 (C-7), 118.7 (C-3′, C-5′), 94.4 (C-4), 64.7 (C-3), 21.1 (CH_3). IR υ_{max} (cm^{-1}, CH_2Cl_2): 3100, 1784, 1515, 816.

Anal. Calcd for $C_{13}H_{10}NO_3Cl$: C, 59.22; H, 3.82; N, 5.31. Found: C, 59.56; H, 3.70; N, 5.22

(3*R*,4*R*,1*R*,2*S*,5*R*:3*S*,4*S*,1*R*,2*S*,5*R*)3-(2-Isopropyl-5-methylcyclohexyloxy)-1-(4-methoxyphenyl)-5-oxa-1-azaspiro[3.4]oct-7-ene-2,6-dione (8b)

The general procedure using *N*-*p*-Methoxyphenylisomaleimide (**1b**) and (-)-menthoxyacetic acid (**7**) was followed to give 30% yield of a 1:1 (3*R*,4*R*,1*R*,2*S*,5*R* : 3*S*,4*S*,1*R*,2*S*,5*R*)-**8b** mixture of mp 119-124 °C. ^{1}H NMR ($CDCl_3$): δ 7.51 (d, J = 5.6 Hz, 1H, H-8); 7.48 (d, J = 5.5 Hz, 1H, H-8); 7.18 (d, J = 8.9 Hz, 2H, H-2', H-6'); 6.79 (d, J = 8.9 Hz, 2H, H-3', H-5'); 6.42 (d, J = 5.6 Hz, 1H, H-7); 5.12, 5.11 (s, 1H, H-3); 3.73 (s, 3H, OMe); 3.39 (td, J = 10.6 Hz, J = 4.0 Hz, 1H, H-1"); 3.21 (td, J = 10.6 Hz, J = 4.0 Hz, 1H, H-1"); 2.22- 2.00 (m, 3H, H-6", H-8"); 1.59-1.61 (br, 4H, H-3", H-4"); 1.33-1.18 (br, 2H, H-2", H-5"); 0.91(d, J = 6.6 Hz, 3H, H-7"); 0.88(d, J = 6.9 Hz, 3H, H-7"); 0.86(d, J = 6.6 Hz, 3H, H-9"); 0.85(d, J = 6.9 Hz, 3H, H-9"); 0.81(d, J = 6.9 Hz, 3H, H-10"); 0.65(d, J = 6.9 Hz, 3H, H-10"). ^{13}C NMR ($CDCl_3$): δ

168.7, 168.6 (C-6), 162.2, 161.8 (C-2), 157.8 (C-4'), 151.7, 151.3 (C-8), 128.3, 128.2 (C-1'), 126.6, 126.5 (C-7), 120.6 (C-2', C-6'), 114.6 (C-3', C-5'), 98.6, 98.5 (C-4), 89.5, 89.3 (C-3), 82.7, 82.5 (C-1"), 55.5 (OCH_3), 47.9, 47.7 (C-5"), 41.3, 41.1 (C-6"), 34.2 (C-3"), 31.5, 31.2 (C-2"), 25.8, 25.5 (C-8"), 23.3, 23.0 (C-4"), 22.2, 22.1 (C-7"), 20.9, 20.8 (C-9"), 16.3, 16.0 (C-10"). IR υ_{max} (cm^{-1}, CH_2Cl_2): 3100, 1774, 1514; Anal. Calcd for $C_{23}H_{29}NO_5$: C, 67.87; H, 7.12; N, 5.25. Found: C, 67.43; H, 6.84; N, 5.28.

(3*R*,4*R*,1*R*,2*S*,5*R*:3*S*,4*S*,1*R*,2*S*,5*R*)-1-(4-Acetoxyphenyl)-3-(2-isopropyl-5-methylcyclohexyloxy)-5-oxa-1-azaspiro[3.4]oct-7-ene-2,6-dione (8c)

The general procedure using (-)-menthoxyacetic acid (**7**) and *N*-*p*-Acetoxyphenylisomaleimide (**1c**) was followed to give 30% yield of the product as a 1:1 (3*R*,4*R*,1*R*,2*S*,5*R* : 3*S*,4*S*,1*R*,2*S*,5*R*)-mixture (**8c**), mp 172-177 °C.

^{1}H NMR ($CDCl_3$): δ 7.53 (d, J = 5.8 Hz, 1H, H-8); 7.50 (d, J = 5.8 Hz, 1H, H-8); 7.28 (d, J = 8.8 Hz, 2H, H-2', H-6'); 7.02 (d, J = 8.8 Hz, 2H, H-3', H-5'); 6.48 (d, J = 5.6 Hz, 1H, H-7); 6.47 (d, J = 5.5 Hz, 1H, H-7); 5.15 (s, 1H, H-3); 3.42 (td, J = 10.6 Hz, J = 4.4 Hz, 1H, H-1"); 3.23 (td, J = 10.6 Hz, J = 4.4 Hz, 1H, H-1"); 2.26 (s, 3H, OAc); 2.21- 2.00 (m, 3H, H-6", H-8"); 1.65-1.61 (br, 4H, H-3", H-4"); 1.33-1.20 (br, 2H, H-2", H-5"); 0.94(d, J = 6.6 Hz, 3H, H-7"); 0.89 (d, J = 6.9 Hz, 3H, H-7"); 0.87 (d, J = 6.6 Hz, 3H, H-9"); 0.86 (d, J = 7.3 Hz, 3H, H-9"); 0.82 (d, J = 6.6 Hz, 3H, H-10"); 0.67 (d, J = 6.9 Hz, 3H, H-10"). ^{13}C NMR ($CDCl_3$): δ 169.3 (C-6), 168.6, 168.5 (O-C=O), 162.2, 161.9 (C-2), 151.5, 151.2 (C-8), 148.2 (C-4'), 133.1, 133.0 (C-1'), 126.9, 126.8 (C-7), 122.7 (C-3',C-5'), 119.5 (C-2', C-6'), 98.4, 98.3 (C-4), 89.7, 89.4 (C-3), 82.9, 82.6 (C-1"), 47.9, 47.7 (C-5"), 41.3, 41.1 (C-6"), 34.3, 34.2 (C-3"), 31.5, 31.4 (C-2"), 25.8, 25.5 (C-8"), 23.3, 23.0 (C-4"), 22.2, 22.1 (C-7"), 21.1 (OAc), 21.0, 20.8 (C-9"), 16.3, 16.0 (C-10"). IR υ_{max} (cm^{-1}, CH_2Cl_2): 3094, 1779, 1509, 1385. (FAB-HRMS) *m*/*z* Calcd for $C_{24}H_{29}NO_6$: 428.2088 Found: *m*/*z* 428.2073.

(3*R*,4*R*,4'*R*:3*S*,4*S*,4'*R*)-3-(2'-Oxo-4'-phenyloxazolidin-3'-yl)-1-phenyl-5-oxa-1-azaspiro[3.4]oct-7-ene 2,6-dione (11a)

The general procedure using (*R*)-(4-phenyloxazolidin-2-one-3-yl)acetic acid (**10**) and *N*-phenylisomaleimide (**1a**) was followed to give 51% yield of a 3:2 mixture of (3*R*,4*R*,4'*R* : 3*S*,4*S*,4'*R*)-**11a**. Fractional crystallization ($CHCl_3$-hexane) of this mixture afforded a 13% yield of (3*S*,4*S*,4'*R*)-**11a** as a white solid, mp 177-180 ºC, $[\alpha]_D^{20}$ - 36.97 (*c* 0.17, $CHCl_3$); and a 26% yield of (3*R*,4*R*,4'*R*)-**11a** as white crystals, mp 225-229 ºC, $[\alpha]_D^{20}$ - 44.86° (*c* 0.44, $CHCl_3$).

(3*R*, 4*R*, 4'*R*)-**11a**. ^{1}H NMR ($CDCl_3$): δ 7.61 (d, J = 5.6 Hz, 1H, H-8); 7.50-7.14 (m, 10H, *arom*); 6.45 (d, J = 5.6 Hz, 1H, H-7); 4.88 (dd, J = 8.8 Hz; J =6.6 Hz, 1H, H-4'); 4.80 (s, 1H, H-3); 4.75 (dd, J = 8.8 Hz, J = 8.8 Hz, 1H, H-5'a); 4.30 (dd, J = 8.8 Hz; J = 6.6 Hz, 1H, H-5'b). ^{13}C NMR ($CDCl_3$): δ 168.4 (C-6),

158.7 (C-2), 157.2 (C-2'), 150.4 (C-8), 136.2 (C-*i*), 135.2 (C-1"), 130.1 (C-*p*), 129.9 (C-3", C-5"), 129.5 (C-*o*), 127.6 (C-7), 127.4 (C-*m*) 126.4 (C-4"); 118.9 (C-2", C-6"); 98.6 (C-4), 71.3 (C-5'), 68.8 (C-3), 60.7 (C-4'). IR υ_{max} (cm^{-1}, CH_2Cl_2): 1777, 1513. Anal. Calcd for $C_{21}H_{16}N_2O_5$: C, 67.02; H, 4.28; N, 7.44. Found: C, 66.83; H, 4.36; N, 7.34.

(3*S*,4*S*,4'*R*)-**11a** ^{1}H NMR($CDCl_3$): δ 7.69 (d, J = 5.7 Hz, 1H, H-8); 7.43-7.13 (m, 10H, arom), 6.21 (d, J = 5.7 Hz, 1H, H-7); 4.89 (dd, J = 8.8 Hz; J =6.6 Hz, 1H, H-4'); 4.79 (dd, J = 8.8 Hz; J = 8.8 Hz, 1H, H-5'a); 4.78 (s, 1H, H-3); 4.38 (dd, J = 8.8 Hz; J = 6.6 Hz, 1H, H-5'b)**.** ^{13}C NMR ($CDCl_3$): δ 167.7 (C-6), 158.9 (C-2), 156.7 (C-2'), 151.0 (C-8), 137.0 (C-*i*), 135.2 (C-1"), 130.4 (C-*p*), 129.9 (C-3", C-5"), 129.4 (C-*o*), 127.1 (C-7, C-*m*), 126.3 (C-4"), 118.9 (C-2", C-6"), 98.3 (C-4), 70.5 (C-5'), 69.6 (C-3), 61.9 (C-4'). IR υ_{max} (cm^{-1}, CH_2Cl_2): 1777, 1513, 1251. Anal. Calcd for $C_{21}H_{16}N_2O_5$: C, 67.02; H, 4.28; N, 7.44. Found: C, 66.83; H, 4.16; N, 7.38.

(3*R*,4*R*,4'*R*:3*S*,4*S*,4'*R*)-1-(4-Methoxyphenyl)-3-(2'-Oxo-4'-phenyloxazolidin-3'-yl)-5-oxa-1-azaspiro-[3.4]oct-7-ene-2,6-dione (11b)

The general procedure using (*R*)-(4-phenyloxazolidin-2-one-3-yl)acetic acid (**10**) and *N*-*p*-methoxyphenylisomaleimide (**1b**) was followed to afford a 90% yield of a 3:2 mixture of (3*R*,4*R*,4'*R* : 3*S*,4*S*,4'*R*)-**11b**.The minor diastereomer (3*S*,4*S*,4'*R*)-**11b** was isolated in pure form by fractional crystallization (hexane-EtOAc) (20% yield) as pale-yellow crystals, mp 215-218 ºC, $[\alpha]_D^{20}$ − 15.71^o (c 0.30, $CHCl_3$).

The major diastereomer (3*R*,4*R*,4'*R*)-**11b** could not be isolated in pure form either by column chromatography or by fractional crystallization. The following NMR data for (3*R*,4*R*,4'*R*)-**11b** are taken from the enriched mixture after two crystallizations. ^{1}H NMR ($CDCl_3$): δ 7.53 (d, J = 5.7 Hz, 1H, H-8); 7.49-7.37 (m, 5H, *o*,*m*,*p*); 7.16 (d, J = 8.8 Hz, 2H, H-2", H-6"); 6.80 (d, J = 8.8 Hz, 2H, H-3", H-5"); 6.38 (d, J = 5.7 Hz, 1H, H-7); 4.88 (dd, J = 8.8 Hz; J = 6.6 Hz, 1H, H-4'); 4.79 (s, 1H, H-3); 4.74 (dd, J = 8.8 Hz; J = 8.8 Hz; 1H, H-5'a); 4.28 (dd, J = 8.8 Hz; J = 6.6 Hz; 1H, H-5'b); 3.75 (s, 3H, OCH_3)**.** ^{13}C NMR ($CDCl_3$): δ 168.3 (C-6), 158.6 (C-2), 158.1 (C-4") 157.2 (C-2'), 150.1 (C-8), 136.2 (C-*i*), 130.0 (C-*p*), 129.9 (C-*m*), 127.5 (C-1"), 127.4 (C-*o*), 127.0 (C-7), 121.6 (C-2", C-6"), 114.6 (C-3", C-5"), 98.7 (C-4), 71.2 (C-5'), 68.5 (C-3), 60.7 (C-4'), 55.4 (OCH_3). IR υ_{max} (cm^{-1}, CH_2Cl_2): 3103, 1776, 1510. Anal. Calcd for $C_{22}H_{18}N_2O_6$: C, 65.02; H, 4.43; N, 6.90. Found: C, 64.95; H, 4.52; N, 6.80.

(3*S*,4*S*,4'*R*)-**11b**: ^{1}H NMR ($CDCl_3$): δ 7.65 (d, J = 5.6 Hz, 1H, H-8); 7.42-7.36 (m, 3H, *m*,*p*); 7.23-7.21 (m, 2H, *o*); 7.17 (d, J = 8.8 Hz, 2H, H-2", H-6"); 6.80 (d, J = 8.8 Hz, 2H, H-3", H-5"); 6.16 (d, J = 5.6 Hz, 1H, H-7); 4.89 (dd, J = 8.8 Hz; J = 6.2 Hz, 1H, H-4'); 4.78 (dd, J = 8.8 Hz; J =8.8 Hz, 1H, H-5'a); 4.76 (s, 1H, H-3), 4.38 (dd, J = 8.8 Hz; J = 6.2 Hz, 1H, H-5'b), 3.74 (s, 3H, OCH_3)**.** ^{13}C NMR ($CDCl_3$): δ 167.9 (C-6), 158.9 (C-2), 158.2 (C-4"), 156.2 (C-2'), 150.0 (C-8), 137.0 (C-*i*), 130.4 (C-*p*) 129.8 (C-*m*), 127.7

(C-1"), 127.1 (C-*o*), 126.9 (C-7), 121.7 (C-2", C-6"), 114.6 (C-3", C-5"), 98.5 (C-4), 70.5 (C-5'), 69.3 (C-3), 61.9 (C-4'), 55.5 (OCH_3). IR υ_{max} (cm^{-1}, CH_2Cl_2): 3107, 1777, 1513. Anal. Calcd for C_{22} H_{18} N_2O_6: C, 65.02; H, 4.43; N, 6.90. Found: C, 65.21; H, 4.50; N, 6.75.

(3*R*,4*R*,4'*R*:3*S*,4*S*,4'*R*)-1-(4-Methylphenyl)-3-(2'-oxo-4'-phenyloxazolidin-3'-yl)-5-oxa-1-azaspiro[3.4]oct-7-ene-2,6-dione (11d)

The general procedure using (*R*)-(4-phenyloxazolidin-2-one-3-yl)acetic acid (**10**) and *N*-*p*-methylphenylisomaleimide (**1d**) was followed to afford a 58% yield of a 2:1 mixture of (3*R*,4*R*,4'*R* : 3*S*,4*S*,4'*R*)-**11d**. This mixture was separated by fractional crystallization (CH_2Cl_2-hexane) to afford a 33% yield of ·(3*R*,4*R*,4'*R*)-**11d** as a white solid, mp 196-198 ºC, $[\alpha]_D^{20}$ -52.56 (*c* 0.06, $CHCl_3$) and a 6% yield of (3*S*,4*S*,4'*R*)-**11d** as white crystals, mp 195-197 ºC $[\alpha]_D^{20}$ -26.59º (*c* 0.06, $CHCl_3$).

(3*R*,4*R*,4'*R*)-**11d**. ^{1}H NMR ($CDCl_3$): δ 7.55 (d, *J* = 5.8 Hz, 1H, H-8); 7.45-7.36 (m, 5H, *o*,*m*,*p*); 7.11 (d, *J* = 8.4 Hz, 2H, H-2", H-6"); 7.07 (d, *J* = 8.4 Hz, 2H, H-3", H-5"); 6.41 (d, *J* = 5.8 Hz, 1H, H-7); 4.89 (dd, *J* = 8.8 Hz; *J* = 6.6 Hz, 1H, H-4'); 4.78 (s, 1H, H-3); 4.74 (dd, *J* = 8.8 Hz; *J* = 8.8 Hz, 1H, H-5'a); 4.27 (dd, *J* = 8.8 Hz; *J* = 6.6 Hz, 1H, H-5'b); 2.28 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$): δ 168.4 (C-6), 158.6 (C-2), 157.2 (C-2'), 150.4 (C-8), 136.4 (C-4"), 132.4 (C-1"), 130.1 (C-*p*), 129.9 (C-3", C-5"), 129.8 (C-*m*), 127.5 (C-7), 127.4 (C-*o*) 127.1 (C-*i*); 119.2 (C-2", C-6"); 98.6 (C-4), 71.3 (C-5'), 68.7 (C-3), 60.7 (C-4'), 21.1 (Me). IR υ_{max} (cm^{-1}, CH_2Cl_2): 3104, 1777, 1753 y 1516. Anal. Calcd for C_{22} $H_{18}N_2O_6$: C, 67.69; H, 4.65; N, 7.18. Found: C, 67.59; H, 4.76; N, 7.17.

(3*S*,4*S*,4'*R*)-**11d.** ^{1}H NMR ($CDCl_3$)**:** δ 7.67 (d, *J* = 5.6 Hz, 1H, H-8); 7.36-7.44 (m, 5H, *o*,*m*,*p*); 7.22 (d, *J* = 8.3 Hz, 2H, H-2", H-6"); 7.09 (d, *J* = 8.3 Hz, 2H, H-3", H-5"); 6.20 (d, *J* = 5.6 Hz, 1H, H-7); 4.88 (dd, *J* = 8.8 Hz; *J* = 6.6 Hz, 1H, H-4'); 4.78 (dd, *J* = 8.8 Hz, *J* = 8.8 Hz 1H, H-5'a); 4.75 (s, 1H, H-3), 4.38 (dd, *J* = 8.8 Hz; *J* = 6.6 Hz, 1H, H-5'b), 2.27 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$): δ 168.8 (C-6), 159.5 (C-2), 158.3 (C-2'), 150.2 (C-8), 136.9 (C-4"), 136.0 (C-1"), 131.5 (C-*p*), 130.3 (C-7), 129.9 (C-3", 5",*m*), 129.8 (C-*i*), 127.0 (C-*o*); 119.2 (C-2", C-6"); 98.9 (C-4), 70.4 (C-5'), 69.0 (C-3), 61.9 (C-4'), 21.2 (Me). IR υ_{max} (cm^{-1}, CH_2Cl_2): 3104, 1777, 1753 y 1516. Anal. Calcd for C_{22} $H_{18}N_2O_6$: C, 67.69; H, 4.65; N, 7.18. Found: C, 67.96; H, 4.88; N, 6.95.

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