

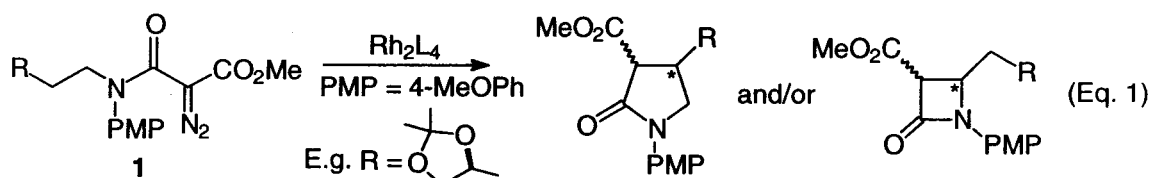
**STUDIES ON THE Rh(II)-CATALYZED C-H INSERTION REACTION OF SOME DERIVATIVES OF *N*-[4-*[(S)*-1,2-DIHYDROXYBUTYL]]- $\alpha$ -DIAZOANILIDES: SITE-SELECTIVITY**

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**Abstract** – The Rh(II)-catalyzed reactions of diazoamides (**1a**, **c-e**) were investigated. The results show that both steric and electronic effects work in concert to govern the regio- and chemo-selectivity of the reaction. The diastereoselectivity of the reaction in the formation of **5a** was determined to be 74% de and the sense of 1,2-induction was found to be *S* at the newly formed C-4 stereogenic centre

In connection with our studies<sup>1</sup> on the Rh(II)-carbenoid mediated asymmetric C–H insertion reaction for the preparation of chiral, non-racemic pyrrolidine compounds,<sup>2</sup> we have examined the C–H insertion in diazo amides, such as **1** (Eq. 1), to determine the regio- and chemoselectivity in the Rh(II)-catalyzed

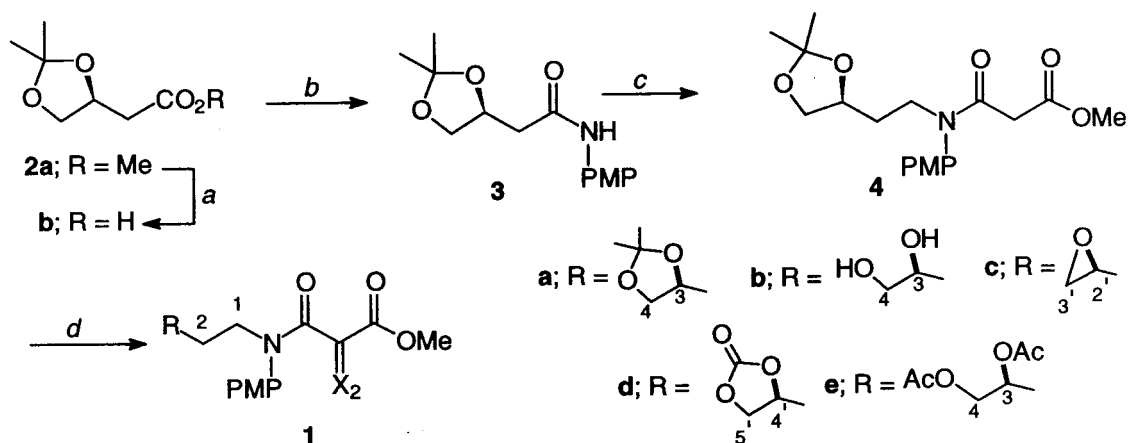


reaction of compounds of type (**1**) as well as to explore whether 1,2-relative induction would be effective for diastereocontrol in  $\gamma$ -lactam formation. Relative asymmetric induction was recently employed in the area of intramolecular rhodium(II)-carbenoid mediated C–H insertion reactions of diazo compounds for the diastereoselective construction of five-membered carbocycles.<sup>3</sup> In these studies,<sup>3</sup> the inducing stereocentre ultimately ends up *endocyclic* to the newly formed ring whereas in system (**1**) (Eq. 1), the inducing centre would end up *exocyclic* to the newly formed ring. We have found that in the present

system, both steric and electronic effects work together to govern the regio- and chemo-selectivity of the reaction. The sense of induction and the diastereoselectivity of the C–H insertion reaction was determined for the  $\gamma$ -lactam (**5a**). It was found that the sense of induction at the new C-4 centre was *S* and the degree of 1,2-asymmetric induction was 74% de.

## RESULTS AND DISCUSSION.

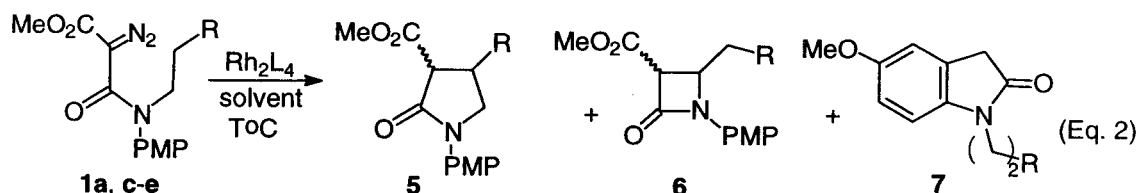
**Preparation of Diazoamides (1a, c-e).** The diazo compounds of type **1** were prepared according to the route as shown in Scheme 1. The known<sup>4</sup> ketal ester (**2a**), prepared from (*S*)-malic acid, was hydrolyzed under basic conditions which, after careful acidification, yielded the ketal acid (**2b**). Condensation of **2b** with 4-methoxyaniline mediated by DCC<sup>5</sup> in the presence of DMAP provided the anilide (**3**).



**Scheme 1:** PMP = *p*-methoxyphenyl. (a) aq. Me<sub>2</sub>C=O, NaOH, rt: 63%; (b) *p*-anisidine, DCC, DMAP, CH<sub>2</sub>Cl<sub>2</sub>: 86%; (c) i; LiAlH<sub>4</sub>, THF, reflux: 98%; ii; MeO<sub>2</sub>CCH<sub>2</sub>CO<sub>2</sub>H, DCC, DMAP, CH<sub>2</sub>Cl<sub>2</sub>: 73%; (d) i; **1a**: KH, DME, MsN<sub>3</sub>, 0 °C: 81%. ii; **1b**: 10:1 MeOH-1M HCl, rt: 92%. iii; **1c**: MsCl, pyridine, EtN(Pr-*i*)<sub>2</sub>, CHCl<sub>3</sub>, 0 °C: 50%; then KOBu-*t*, THF, 0 °C: 94%. iv; **1d**: 4-NO<sub>2</sub>PhOC(=O)Cl, DMAP, MeCN, rt, 22 h, 89%; v; **1e**: Ac<sub>2</sub>O, DMAP, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, rt, 95%.

Reduction of **3** with LiAlH<sub>4</sub> led to the corresponding aniline derivative which was reacted with  $\alpha$ -(carbomethoxy)acetic acid to give the ester amide (**4**). Subsequent diazotization using methanesulfonyl azide<sup>6</sup> (MsN<sub>3</sub>) in the presence of KH<sup>7a</sup> gave the diazoamide (**1a**). Compound (**1a**) served as the key intermediate for the preparation of diazo compounds (**1c-e**). Thus mild acid hydrolysis of the ketal protecting group in **1a** gave the corresponding diol (**1b**). Selective mesylation of the primary hydroxyl in **1b** followed by treatment with base gave the epoxide (**1c**) in 44% yield (2 steps). Compound (**1d**) was obtained in 89% yield *via* carbonation of **1b** using *p*-nitrophenyl chloroformate. Diacetylation of the diol (**1b**) proceeded efficiently (95%) to furnish diazo compound (**1e**).

*Rhodium(II)-Catalyzed Reaction of 1a, c-e.* The Rh(II)-catalyzed reaction of diazo compound (**1a**) (Eq. 2) under different reaction conditions (solvent, temperature, Rh(II) catalyst) was first studied to determine the regio- and chemoselectivity of the reaction (Eq. 2). The results are summarized in Table 1.



**TABLE 1:** Regio- and Chemoselectivity of Rh<sub>2</sub>L<sub>4</sub> Catalyzed Reactions of Diazoamides (**1a, c-e**).

Entry	compd	Rh <sub>2</sub> L <sub>4</sub> <sup>a</sup>	solvent	temp. °C	yield%	5 : 6 : 7 <sup>d,e</sup>
1	<b>1a</b>	Rh <sub>2</sub> (OAc) <sub>4</sub>	CH <sub>2</sub> Cl <sub>2</sub>	30	75	1 : 1 : 0
2	<b>1a</b>	Rh <sub>2</sub> (OAc) <sub>4</sub>	CH <sub>2</sub> Cl <sub>2</sub>	45	64	1 : 1.5 : 0
3	<b>1a</b>	Rh <sub>2</sub> (OAc) <sub>4</sub>	PhH	25	82	1 : 1.2 : 0
4	<b>1a</b>	Rh <sub>2</sub> (OAc) <sub>4</sub>	PhH	80	60	1 : 2.4 : 0
5	<b>1a</b>	Rh <sub>2</sub> (Oct) <sub>4</sub>	CH <sub>2</sub> Cl <sub>2</sub>	25	65	1 : 1.7 : 0
6	<b>1a</b>	Rh <sub>2</sub> (Piv) <sub>4</sub>	PhH	80	56	1 : 5 : 0
7	<b>1a</b>	Rh <sub>2</sub> (R-PTPA) <sub>4</sub>	CH <sub>2</sub> Cl <sub>2</sub>	30	47	0 : 1 : 1.5
8	<b>1c</b>	Rh <sub>2</sub> (OAc) <sub>4</sub>	CH <sub>2</sub> Cl <sub>2</sub>	30	63	1 : 1.2 : 0
9	<b>1d</b>	Rh <sub>2</sub> (OAc) <sub>4</sub>	PhH	30	55	1 : 5 <sup>b</sup> : 0
10	<b>1e</b>	Rh <sub>2</sub> (R-PTPA) <sub>4</sub>	(CH <sub>2</sub> Cl) <sub>2</sub>	30	77	0 : 2.4 : 1
11	<b>1e</b>	Rh <sub>2</sub> (R-PTPA) <sub>4</sub>	(CH <sub>2</sub> Cl) <sub>2</sub>	60	78	0 : 1.3 : 1
12	<b>1a</b>	Rh <sub>2</sub> (acam) <sub>4</sub>	PhH	80	17 <sup>c</sup>	0 : 0 : 1
13	<b>1d</b>	Rh <sub>2</sub> (acam) <sub>4</sub>	CH <sub>2</sub> Cl <sub>2</sub>	30	97 <sup>c</sup>	0 : 0 : 1

a) See experimental section for names of Rh(II) catalyst. b) Compounds (**5d:6d**) were obtained as an inseparable mixture; ratio was determined by integration of the H-3 doublet in **5d** ( $\delta$  3.49) and **6d** ( $\delta$  3.98; 4.02) c) No  $\gamma$ - and  $\beta$ - lactams (**5** and **6**) were detected but the oxindole product (**7**) was obtained. d) Ratios were based on isolated yields. e) Compounds (**7**) are readily characterized by <sup>1</sup>H NMR: the singlet at  $\delta$  3.50 due to the C-3 methylene hydrogens as well as the three proton resonances of the aromatic hydrogens. In the IR spectrum, the oxindole  $\nu$  (C=O) absorbs at 1704–1707 cm<sup>-1</sup>.

The data reveal that the nature of the solvent had no influence on the regioselectivity of the reaction (Entries 1 and 3). On the other hand, reaction temperature had a strong influence on regioselectivity

(compare Entries 1, 2; 3, 4); there was a two-fold increase in the preference for  $\beta$ -lactam (**6**) when the reaction was conducted in refluxing benzene (Entries 3, 4).

Unlike the usual high preference for  $\gamma$ -lactam formation observed in the  $\text{Rh}_2(\text{OAc})_4$ -catalyzed intramolecular C–H insertion in other diazoanilide systems,<sup>7</sup> the present system furnished a mixture of  $\gamma$ - and  $\beta$ -lactams (**5**) and (**6**) (Entries 1–4). As the steric size of the dirhodium(II) catalyst was increased, there was an increase in the preference for the formation of  $\beta$ -lactam (**6**) (Entries 1,5; 4,6). A combined use of a higher reaction temperature and a bulky Rh(II) catalyst resulted in the predominate formation of **6** (Entry 6). With bulkier catalysts such as  $\text{Rh}_2(R\text{-PTPA})_4$ <sup>8</sup> the  $\gamma$ -lactam formation pathway is completely “shut-down”; only  $\beta$ -lactam (**6a**) and the oxindole (**7a**) were obtained (Entry 7).

With **1c**, wherein the oxiranyl moiety is a relatively smaller size group compared to the dioxolanyl unit in **1a**, almost equal amounts of **5c**:**6c** was obtained (compare Entries 1 and 8). This result is similar to that obtained for **1a**, which suggests that electronic effects in addition to the steric effects noted above also govern the regioselectivity of the reaction.

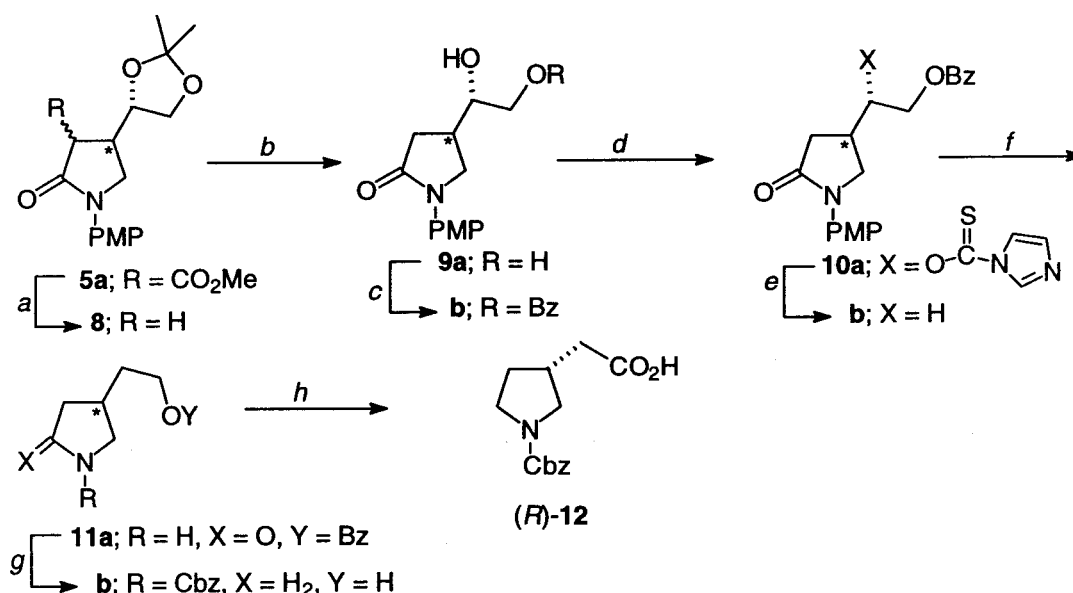
A more dramatic demonstration of electronic effect on the regioselectivity of the C-H insertion was provided by the reaction of **1d** (Entry 9). Its  $\text{Rh}_2(\text{OAc})_4$ -catalyzed reaction led to a predominate formation of the  $\beta$ -lactam (**6d**). As well, the use of the carbonate group and  $\text{Rh}_2(\text{OAc})_4$  had the same overall outcome as using a dioxolanyl group with  $\text{Rh}_2(\text{Piv})_4$  (compare Entries 6 and 9). In **1e**, the diacetate unit is conformationally more mobile than the carbonate group in **1d** and it was expected that steric effects would, therefore, be minimal. However, we surmised that the electronic effects would be similar to that in **1d** and  $\beta$ -lactam formation would be strongly favoured. Reaction of **1e** with  $\text{Rh}_2(R\text{-PTPA})_4$  led to  $\beta$ -lactam (**6e**) as well as the oxindole (**7e**); the  $\gamma$ -lactam (**5e**) was not detected at all (Entries 10 and 11). Interestingly, increasing the reaction temperature resulted in a significant decrease in the yield of **6e** (Entry 11).

The use of the “electronically selective”<sup>9</sup>  $\text{Rh}_2(\text{acam})_4$  with compound (**1a**) did not lead to the formation of **5a** and **6a**, but instead afforded a low yield (17%) of the oxindole (**7a**) (Entry 12). With **1d**, however, a high yield of **7d** was obtained (Entry 13).

The above composite results suggest that steric as well as electronic effects govern the regio- and chemo-selectivity of the reaction. Bulky R groups, such as the dioxolanyl moiety, can sterically shield the target C-H site for  $\gamma$ -lactam formation from attack by the Rh(II)-carbenoid intermediate. This would allow  $\beta$ -lactam formation to compete effectively with  $\gamma$ -lactam formation. The results from experiments where bulky catalysts (e.g.,  $\text{Rh}_2(\text{Piv})_4$ ,  $\text{Rh}_2(R\text{-PTPA})_4$ ) were used are in accord with this “steric” reasoning; there was a marked increase in preference for formation of compound (**6**) and  $\gamma$ -lactam formation had become a minor reaction pathway. In cases where  $\gamma$ -lactam formation was no longer competitive, an alternative

reaction pathway was observed, namely, electrophilic attack of the Rh(II)-carbenoid onto the activated, sterically more accessible *N*-PMP unit to give oxindole (7).

The methylene hydrogens that are directly adjacent to the R group in **1** are deactivated (less nucleophilic) by the electron-withdrawing inductive effect of the oxygen substituent(s); however, the methylene hydrogens that are adjacent to the amide nitrogen are not deactivated as much because of the activating influence of the amide nitrogen.<sup>7</sup> This notion is supported by the observation that in the reaction of **1**, compounds (**5**) and (**6**) are formed in almost equal amounts and in some cases there was a slight preference for **6**. That is,  $\beta$ -lactam formation competes effectively with  $\gamma$ -lactam formation. Upon using a strongly electronwithdrawing carbonate group (**1d**), Rh(II)-carbenoid C–H insertion occurs in favour of  $\beta$ -lactam formation. The preference for oxindole formation with Rh<sub>2</sub>(acam)<sub>4</sub> can be attributed to the less electrophilic and more selective nature of the Rh<sub>2</sub>(acam)<sub>4</sub>-carbenoid. Consequently, it would react with the site of higher electron density, in this case the *N*-PMP moiety.

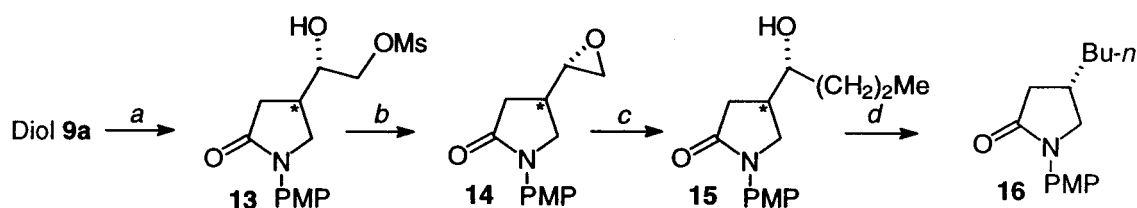


**Scheme 2.** (a) NaCl, aq. DMSO, reflux; 92%; (b) 10:1 MeOH:1M HCl, rt; 82%; (c) PhC(=O)Cl, CH<sub>2</sub>Cl<sub>2</sub>, pyridine; 97%; (d) 1,1'-thiocarbonyldiimidazole, (CH<sub>2</sub>Cl)<sub>2</sub>; 86%; (e) n-Bu<sub>3</sub>SnH, AIBN, PhMe, reflux; 82%; (f) CAN, 2:1 MeCN-H<sub>2</sub>O, 0 °C; 81%; (g) LiAlH<sub>4</sub>, THF, reflux; then 1M NaOH Cbz-Cl; 66%; (h) Jones' reagent, Me<sub>2</sub>C=O, 0 °C, 88%.

*Sense and Degree of Asymmetric Induction.* Our failure to satisfactorily decarboxylate **6a** without destruction of the  $\beta$ -lactam ring prevented us from determining the sense and degree of 1,3 induction for **6a**. Nevertheless, HPLC analysis and separation of **6a** indicated that only two diastereomers were formed. The relative stereochemistry of the C-3 and C-4 substituents in both diastereomers was assigned as *trans*<sup>10</sup>

on the basis of the characteristic vicinal coupling constant  $J_{3,4} = 2.5 \text{ Hz}^{7,10,11}$  of the H-3 doublet.

We then turned our attention to determining the sense and degree of 1,2-asymmetric induction in the formation of **5a**, and this entailed the preparation of 3-(*N*-Cbz-pyrrolidinyl)acetic acid (**12**) (Scheme 2) and *N*-PMP-4-butyl-2-pyrrolidinone (**16**) (Scheme 3). The synthesis of **12** began with the decarboxylation of **5a** (Entry 1) to give the  $\gamma$ -lactam (**8**) (Scheme 2). Acid hydrolysis of the ketal unit furnished the diol (**9a**) that was subjected to selective benzylation to provide the monobenzoate (**9b**). Treatment of **9b** with excess 1,1'-thiocarbonyldiimidazole furnished the imidazolidone (**10a**), which was reduced with *n*-Bu<sub>3</sub>SnH<sup>12</sup> to afford **10b**. Deprotection of the *N*-PMP group in **10b** using CAN gave the very polar  $\gamma$ -lactam (**11a**) that was immediately reduced with LiAlH<sub>4</sub> to provide the corresponding amino alcohol. Without purification, the amino alcohol was acylated at nitrogen with Cbz-Cl to provide the 3-(*N*-Cbz-pyrrolidinyl)ethanol (**11b**). Jones' oxidation of the primary alcohol gave 3-(*N*-Cbz-pyrrolidinyl)acetic acid (**12**). Comparison of the specific optical rotation of **12**,  $[\alpha]_D^{22} -13^\circ$  (*c*, 1.6, CHCl<sub>3</sub>), with that of the recently reported<sup>13</sup> (*S*)-**12**  $\{[\alpha]_D^{20} + 21^\circ$  (*c* 0.5, CHCl<sub>3</sub>) $\}$  showed that the configuration of the new stereocentre is *R*.



**Scheme 3:** (a) MsCl, *i*-Pr<sub>2</sub>NEt, pyridine, CHCl<sub>3</sub>; 98%; (b) *t*-BuOK, THF, rt; 78%; (c) Et<sub>2</sub>CuLi, Et<sub>2</sub>O, -78 to -35 °C; 85%; (d) PhOC(=S)Cl, DMAP, MeCN; 49%; then *n*-Bu<sub>3</sub>SnH, AIBN, PhMe, 80 °C; 98%.

Independent support for the assignment of the stereochemistry at the new C-4 centre was derived from the chiral HPLC analysis of compound (**16**) (Scheme 3). The preparation of **16** started from the diol (**9a**). Selective mesylation followed by base treatment furnished the epoxide (**14**). Treatment of **14** with Et<sub>2</sub>CuLi in ether gave the secondary alcohol (**15**), which was deoxygenated according to Robins' procedure<sup>14</sup> to give the desired **16**. HPLC analysis of compound (**16**) on a Chiralcel OB column (70:30 hexanes:2-propanol) and comparison of its *t*<sub>R</sub> to that of the known reference (*S*)-**16**<sup>1a</sup> indicated that the absolute configuration at C-4 is *S*. The analysis also showed that the degree (*de*) of asymmetric induction at C-4 is 74%. Together the above results indicate that the sense of induction at the newly created C-4 stereocentre in **5a** is the same as that in the inducing centre; that is, the configuration of the C-4 stereocentre is *S* when the inducing stereocentre is *S*. As well, good diastereoselectivity was achieved

during the key bond formation step.

## CONCLUSIONS

Both steric and electronic factors work together to govern the regio- and chemoselectivity of the Rh(II)-carbenoid C–H insertion reaction in system of type (1). Rh(II) catalysts that possess bulky ligands favoured  $\beta$ -lactam formation. On the other hand, chiral Rh(II) catalysts, whose ligands are bulkier promoted  $\beta$ -lactam and oxindole formation. In the case of  $\gamma$ -lactam (5a), a good level (74%) of 1,2-asymmetric induction was realized. The sense of induction at the newly formed C-4 in the reaction of 1a is *S* when the inducing stereocentre is *S*.

## EXPERIMENTAL

General: Melting points were determined on an Electrothermal IA9100 digital melting point apparatus and are uncorrected. IR spectra were recorded using a Perkin-Elmer 1600FT infrared spectrophotometer and only diagnostic signals are reported. NMR spectra were obtained on a Bruker AC200 QNP spectrometer:  $^1\text{H}$  NMR ( $\delta_{\text{TMS}} = 0$ ) and  $^{13}\text{C}$  NMR ( $\delta_{\text{CDCl}_3} = 77.00$ ) spectra were obtained in  $\text{CDCl}_3$  at 200 MHz and at 50 MHz, respectively. Where appropriate the signals of minor diastereomers in products are cited within brackets. Optical rotations were measured on an Optical Activity (AA-5) polarimeter. High resolution MS and elemental analyses were performed at the Department of Chemistry, University of Saskatchewan. Reaction progress was monitored by TLC using Merck<sup>®</sup> silica gel 60<sub>F254</sub> precoated (0.25mm) on aluminum-backed sheets. Purification is by flash chromatography<sup>15</sup> unless otherwise stated, and was performed on Merck<sup>®</sup> silica gel 60 (230-400 mesh). Compounds were obtained as oils, unless stated otherwise. Petroleum ether used is the fraction with bp 35-60 °C. All air and moisture sensitive reactions were carried out under a static pressure of argon. All organic extracts were dried over anhydrous  $\text{Na}_2\text{SO}_4$ . Acetone was dried by distillation from  $\text{KMnO}_4$ .  $\text{CH}_2\text{Cl}_2$ ,  $\text{ClCH}_2\text{CH}_2\text{Cl}$ , MeCN, toluene, benzene, pyridine and  $\text{Et}_3\text{N}$  were dried by distillation from  $\text{CaH}_2$ . DME was dried by refluxing it over  $\text{CaH}_2$  for a minimum of 36 h, followed by distillation from  $\text{CaH}_2$ . MeOH was dried by distillation from magnesium methoxide.  $\text{Et}_2\text{O}$  and THF were dried by distillation from sodium using sodium benzophenone ketyl as an indicator. Abbreviations used for Rh(II) catalysts:  $[\text{Rh}_2(\text{Oct})_4]$ : rhodium(II) octanoate;  $[\text{Rh}_2(\text{Piv})_4]$ : rhodium(II) pivalate;  $[\text{Rh}_2(\text{acam})_4]$ : rhodium(II) acetamidate;  $[\text{Rh}_2(\text{R-PTPA})_4]$ : rhodium(II) (*R*)-*N*-phthaloylphenylalaninate.

(*S*)-*N*-(4-Methoxyphenyl)-3,4-dihydroxy-3,4-*O*-isopropylidenebutanamide (3). The ester (2a)<sup>4</sup> was dissolved in acetone (78 mL) and cooled to 0 °C. A solution of NaOH (1.9 g, 47.6 mmol) in water (62

mL) was added slowly over 20 min to the ester solution. After 45 min, the reaction mixture was concentrated and solid NaCl was added. The mixture was washed with CH<sub>2</sub>Cl<sub>2</sub> to remove mesityl oxide. Then the mixture was cooled to 0 °C and 1 M aqueous HCl was carefully added until a pH of ~3 was reached. The acidified mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> (4 x 50 mL) and the combined extracts were dried, filtered and concentrated. The residue was subjected to Kugelrohr distillation, 98 °C (oven temp) at 0.1 Torr, to provide 4.16 g (63%) of **2b**. [ $\alpha$ ]<sub>D</sub><sup>22</sup> +5.8 ° (c, 4.3, CHCl<sub>3</sub>).  $\nu_{\max}$ : 3718–2300, 1718 cm<sup>-1</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  1.37 (s, 3H, Me), 1.43 (s, 3H, Me), 2.58 (dd, 1H, *J* = 16.3, 7 Hz, H-2), 2.75 (dd, 1H, *J* = 16.2, 7 Hz, H-2'), 3.68 (dd, 1H, *J* = 8.2, 2.1 Hz, H-4), 4.17 (dd, 1H, *J* = 6.3, 2.5 Hz, H-4'), 4.48 ("quintet", 1H, *J* = 6.2 Hz, H-3), 9.4–10.6 (br s, 1H, OH). <sup>13</sup>C NMR (CDCl<sub>3</sub>):  $\delta$  25.4, 26.8, 38.8, 68.9, 71.7, 109.4, 176.2.

4-Methoxyaniline (3 g, 24.3 mmol) and DMAP (0.228 g, 10 mol%) were dissolved in CH<sub>2</sub>Cl<sub>2</sub> (18 mL) and the resulting solution was cooled to 0 °C. A solution of the acid (**2b**) (3 g, 18.7 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (10 mL) was then added dropwise, *via* cannula, followed by a solution of DCC (3.86 g, 22.4 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (5 mL). The mixture was stirred at 0 °C for 15 min and then at rt overnight. The urea precipitate was filtered off and the residue washed twice with CH<sub>2</sub>Cl<sub>2</sub> (15 mL). The combined filtrates were washed with 1M aqueous HCl (3 x 10 mL), saturated NaHCO<sub>3</sub> (3 x 10 mL) and brine (20 mL). The organic phase was dried, filtered, evaporated and the residue was purified (pet. ether–EtOAc, 3:1) to give crystalline (**3**) (4.3 g, 86%). mp 184–187 °C, [ $\alpha$ ]<sub>D</sub><sup>22</sup> -10.3 ° (c, 5.3, CHCl<sub>3</sub>). IR  $\nu_{\max}$ : 3321, 1666 cm<sup>-1</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  1.40 (s, 3H, Me), 1.48 (s, 3H, Me), 2.64 ("q", 2H, *J* = 6.9 Hz, 2H-2), 3.68 (dd, 1H, *J* = 8.2, 1.5 Hz, H-4), 3.78 (s, 3H, OMe), 4.17 (dd, 1H, *J* = 8.2, 2.2 Hz, H-4'), 4.50 ("quintet", 1H, *J* = 6.7 Hz, H-3), 6.85 (d, 2H, *J* = 6.6 Hz, Ar H), 7.41 (d, 2H, *J* = 6.6 Hz, Ar H), 8.04–8.17 (br s, 1H, N-H). <sup>13</sup>C NMR (CDCl<sub>3</sub>):  $\delta$  25.5, 26.9, 41.1, 55.4, 69.0, 72.4, 109.5, 113.8, 114.0, 121.8, 130.8, 168.1. Anal. Calcd for C<sub>14</sub>H<sub>19</sub>NO<sub>4</sub>: C, 63.38; H, 7.22; N, 5.28. Found: C, 63.45; H, 7.27; N, 5.42.

***N*-[*[(S)*-3,4-Dihydroxy-3,4-*O*-isopropylidene]butyl]-*N*-(4-methoxyphenyl)- $\alpha$ -**

**(carbomethoxy)acetamide (4)**. The amide (**3**) (3.1 g, 11.6 mmol) was dissolved in THF (100 mL) and the mixture was cooled to 0 °C. LiAlH<sub>4</sub> (1.32 g, 35 mmol) was added to the reaction mixture in one portion. The mixture was stirred at 0 °C until gas evolution subsided and then the reaction mixture was refluxed. After 17 h, the reaction mixture was cooled to 0 °C and water was carefully added to destroy excess LiAlH<sub>4</sub> and was followed by 10% aqueous NaOH (60 mL) and solid NaCl. The mixture was extracted with ether (4 x 50 mL). The combined ethereal extracts were dried, filtered, evaporated and purified (pet. ether–EtOAc, 4:1) to provide the slightly unstable amine (2.9 g, 98%). This amine was used immediately in the next step. IR  $\nu_{\max}$ : 3390 cm<sup>-1</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  1.38 (s, 3H, Me), 1.44 (s, 3H, Me),



1.87 ("q", 2H,  $J = 6.4$  Hz, 2H-2), 3.22 (t, 2H,  $J = 6.9$  Hz, H-1), 3.57 (m, 1H, H-4), 3.75 (s, 3H, OMe), 4.02-4.31 (m, 2H, H-3, H-4'), 6.59 (d, 2H,  $J = 8.8$  Hz, Ar H), 6.78 (d, 2H,  $J = 8.8$  Hz, Ar H).

The above amine (2.1 g, 8.33 mmol) was reacted with  $\alpha$ -(carbomethoxy)acetic acid (1.28 g, 10.8 mmol) in the presence of DCC (2.22 g, 10.8 mmol) and catalytic amounts of DMAP (0.101 g, 0.833 mmol) according to the procedure described for the preparation of **3**. The yield of the amide (**4**), after purification (pet. ether–EtOAc, 3:1), was 2.97 g (73%).  $[\alpha]_{\text{D}}^{23} +7.73^\circ$  (*c*, 3.86, CHCl<sub>3</sub>). IR  $\nu_{\text{max}}$ : 1745, 1660 cm<sup>-1</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  1.33 (s, 3H, Me), 1.37 (s, 3H, Me), 1.75–1.91 (m, 2H, H-2), 3.19 (s, 2H, CH<sub>2</sub>(C=O)<sub>2</sub>), 3.45-3.93 (m, 3H, H-1, H-4), 3.67 (s, 3H, OMe), 3.83 (s, 3H, OMe), 4.00–4.23 (m, 2H, H-3, H-4'), 6.92 (d, 2H,  $J = 8.8$  Hz, Ar H), 7.13 (d, 2H,  $J = 8.8$  Hz, Ar H). <sup>13</sup>C NMR (CDCl<sub>3</sub>):  $\delta$  25.5, 26.9, 31.5, 41.5, 46.6, 52.2, 55.5, 69.2, 73.8, 108.8, 114.9, 129.2, 134.4, 159.3, 168.2. Anal. Calcd for C<sub>18</sub>H<sub>25</sub>NO<sub>6</sub>: C, 61.52; H, 7.17; N, 3.99. Found: C, 61.73; H, 7.34; N, 3.91.

***N*-[*(S)*-3,4-Dihydroxy-3,4-*O*-isopropylidene]butyl]-*N*-(4-methoxyphenyl)- $\alpha$ -carbomethoxy- $\alpha$ -**

**diazoacetamide (1a)**. A suspension of KH (2.08 g, 18.2 mmol; 35 % dispersion in mineral oil, prewashed with DME) in DME (10 mL) was cooled to 0 °C. A solution of the amide (**4**) (3.18 g, 9.1 mmol) in DME (5 mL) was added dropwise *via* cannula. At this point hydrogen gas evolution was observed. The mixture was stirred for five min and then MsN<sub>3</sub> (1.5 mL, 18.2 mmol) was added to the mixture; a yellow color developed immediately. After 4 h, the reaction mixture was quenched at 0 °C by the careful addition of water (5 mL). The organic layer was washed with brine (3 X 20 mL), dried, filtered, evaporated and purified (pet. ether–EtOAc, 2:1) to afford diazoamide (**1a**) (2.76 g, 81%).  $[\alpha]_{\text{D}}^{21} +13^\circ$  (*c*, 1.73, CHCl<sub>3</sub>).  $\nu_{\text{max}}$ : 2119, 1732, 1690 cm<sup>-1</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  1.32 (s, 3H, Me), 1.36 (s, 3H, Me), 1.74–1.95 (m, 2H, 2H-2), 3.55 (dd, 1H,  $J = 7.5, 6.4$  Hz, H-1), 3.63 (s, 3H, OMe), 3.68-4.21 (m, 4H, H-1, H-3, 2H-4), 3.82 (s, 3H, OMe), 6.89 (d, 2H,  $J = 9.0$  Hz, Ar H), 7.12 (d, 2H,  $J = 9.0$  Hz, Ar H). <sup>13</sup>C NMR (CDCl<sub>3</sub>):  $\delta$  25.55, 26.88, 31.46, 48.18, 52.24, 55.46, 69.13, 73.77, 108.90, 114.70, 127.95, 134.64, 158.56, 160.40, 162.83. Anal. Calcd for C<sub>18</sub>H<sub>23</sub>N<sub>3</sub>O<sub>6</sub>: C, 57.29; H, 6.14; N, 11.13. Found: C, 57.51; H, 6.35; N, 11.12.

***N*-[*(S)*-3,4-Dihydroxybutyl]-*N*-(4-methoxyphenyl)- $\alpha$ -carbomethoxy- $\alpha$ -diazoacetamide (1b)**. The ketal (**1a**) (184 mg, 0.488 mmol) was dissolved in a mixture of MeOH:1M aqueous HCl solution (10:1 v/v, 20 mL) and stirred at rt for 1 h. The solvent was evaporated *in vacuo*. The residue was taken into CH<sub>2</sub>Cl<sub>2</sub> (25 mL) and dried with a 1:1 mixture of anhydrous Na<sub>2</sub>SO<sub>4</sub> and K<sub>2</sub>CO<sub>3</sub>. The solution was filtered, concentrated and purified (20:1 CH<sub>2</sub>Cl<sub>2</sub>:MeOH) to give the diol (**1b**) (92 %, 152 mg).  $[\alpha]_{\text{D}}^{22} +43^\circ$  (*c*, 7, CHCl<sub>3</sub>).  $\nu_{\text{max}}$ : 3671–3107, 2121, 1729 cm<sup>-1</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  1.43–1.70 (m, 2H, 2H-2), 2.10–2.29 (br s, 1H, OH), 2.68–2.97 (br. s, 1H, OH), 3.30–3.88 (m, 4H, 2H-1, 2H-4), 3.62 (s, 3H, OMe), 3.82 (s, 3H, OMe), 4.15–4.41 (m, 1H, H-3), 6.90 (d, 2H,  $J = 9.1$  Hz, Ar H), 7.11 (d, 2H,  $J = 9.1$  Hz, Ar H). <sup>13</sup>C NMR

(CDCl<sub>3</sub>):  $\delta$  30.7, 47.9, 52.3, 55.5, 66.5, 68.5, 114.9, 127.8, 133.7, 158.8, 161.8, 162.3. This diol was characterized as its diacetate (**1e**).

**N-(4-Methoxyphenyl)-N-[2-((S)-2-oxiranyl)ethyl]- $\alpha$ -carbomethoxy- $\alpha$ -diazoacetamide (1c).** The diol (**1b**) (405 mg, 1.2 mmol) was dissolved in dry CHCl<sub>3</sub> (6 mL) containing dry pyridine (0.388 mL, 4.81 mmol) and (*i*-Pr)<sub>2</sub>NEt (0.105 mL, 0.6 mmol). The mixture was cooled to 0 °C and methanesulfonyl chloride (0.118 mL, 1.5 mmol) was added dropwise to the mixture. After a brief period at 0 °C, the mixture was stirred at rt for 18 h. The reaction mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub> (10 mL) and washed successively with water (10 mL), saturated CuSO<sub>4</sub> solution (2 x 10 mL), water (10 mL) and saturated NaHCO<sub>3</sub> (10 mL). The organic phase was dried, filtered and evaporated to leave an oil which was purified by chromatography (CH<sub>2</sub>Cl<sub>2</sub>-acetone, 8:1) to provide the desired monomesylate (232 mg, 50 %). IR  $\nu_{\max}$ : 3589–3260, 2120, 1725, 1690, 1624, 1511 cm<sup>-1</sup>. <sup>1</sup>H NMR,  $\delta$ : 1.45–1.65 (m, 2H, 2H-2), 3.05 (s, 3H, MeSO<sub>2</sub>), 3.56 (s, 3H, OMe), 3.50–3.68 (m, 1H, H-1), 3.78 (s, 3H, OMe), 3.82–4.00 (m, 1H, H-1'), 4.15 (d, 2H, *J* = 4.8 Hz, 2H-4), 4.20–4.40 (m, 2H, H-3, OH), 6.88 (d, 2H, *J* = 7.2 Hz, ArH), 7.05 (d, 2H, *J* = 7.2 Hz, ArH).

The above monomesylate (220 mg, 0.53 mmol) was dissolved in dry THF (8 mL) and the solution was cooled to 0 °C. Potassium *tert*-butoxide (66 mg, 0.583 mmol) was added and the mixture was stirred at 0 °C for 1 h. Ethyl acetate (10 mL) followed by saturated NH<sub>4</sub>Cl solution (1 mL) was added to the reaction mixture. The organic phase was separated and the aqueous phase was reextracted with EtOAc (2 x 5 mL). The combined organic phases were washed with brine (10 mL), dried, filtered and evaporated to leave an oil. Purification of the oily product (pet. ether EtOAc, 2:1 and then 1:1) gave 160 mg (94%) of the epoxide (**1c**). [ $\alpha$ ]<sub>D</sub><sup>21</sup> -2.3 ° (*c* 1.1, CHCl<sub>3</sub>). IR  $\nu_{\max}$ : 3051, 2118, 1728, 1690, 1636, 1511 cm<sup>-1</sup>. <sup>1</sup>H NMR,  $\delta$ : 1.52–1.77 (m, 1H, H-2), 1.80–2.02 (m, 1H, H-2'), 2.40 (dd, 1H, *J* = 5.4, 3.1, H-3''), 2.68 ("t", 1H, *J* = 4.7, H-3''), 2.86–2.98 (m, 1H, H-2''), 3.58 (s, 3H, OMe), 3.77 (s, 3H, OMe), 3.75–3.98 (m, 2H, 2H-1), 6.85 (d, 2H, *J* = 7.2 Hz, ArH), 7.1 (d, 2H, *J* = 7.2 Hz, ArH). <sup>13</sup>C NMR,  $\delta$ : 30.6, 46.6, 48.0, 50, 5.1, 55.3, 114.6, 127.9, 134.4, 158.5, 160.3, 162.6.

**N-[2-((S)-4-(2-Oxo-1,3-dioxolanyl)ethyl)-N-(4-methoxyphenyl)- $\alpha$ -carbomethoxy- $\alpha$ -diazoacetamide (1d).** The diol (**1b**) (131 mg, 0.387 mmol) and DMAP (127 mg, 1.04 mmol) were dissolved in MeCN (8 mL). 4-Nitrophenyl chloroformate (260 mg, 1.02 mmol) was dissolved in MeCN (4 mL) and transferred to the diol solution *via* cannula. The reaction mixture was stirred for 22 h and the solvent was evaporated. The residue was purified (CH<sub>2</sub>Cl<sub>2</sub>:acetone, 10:1) to give the cyclic carbonate (**1d**) (89 %, 125 mg). IR  $\nu_{\max}$ : 2119, 1795, 1729, 1689, 1510 cm<sup>-1</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  1.99 ("q", 2H, *J* = 6.9 Hz, 2H-2), 3.58 (s, 3H, OMe), 3.65–4.04 (m, 2H, 2H-1), 3.79 (s, 3H, OMe), 4.10 (dd, 1H, *J* = 8.6, 6.9 Hz, H-5''), 4.56 (t, 1H,

$J = 8.6$  Hz, H-5"), 4.78 ("quintet", 1H,  $J = 6.9$  Hz, H-4"), 6.87 (d, 2H,  $J = 9.0$  Hz, Ar H), 7.08 (d, 2H,  $J = 9.0$  Hz, Ar H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  32.0, 46.9, 55.3, 55.6, 65.67, 69.3, 75.0, 115.0, 127.9, 134.0, 154.8, 158.9, 161.0, 162.4. Anal. Calcd for  $\text{C}_{16}\text{H}_{17}\text{N}_3\text{O}_7$ : C, 52.89; H, 4.72; N, 11.57. Found: C, 52.94; H, 4.76; N, 11.51.

***N*-[(*S*)-3,4-Diacetoxybutyl]-*N*-(4-methoxyphenyl)- $\alpha$ -carbomethoxy- $\alpha$ -diazoacetamide (1e).** The diol (1b) (127 mg, 0.375 mmol) and DMAP (15 mg, 0.123 mmol) were dissolved in  $\text{CH}_2\text{Cl}_2$  (0.5 mL) and  $\text{Et}_3\text{N}$  (0.3 mL) was added followed by  $\text{Ac}_2\text{O}$  (0.25 mL). The reaction was stirred at rt for 18 h then the solvent was removed *in vacuo*. The residue was subjected to column chromatography (3:1 then 1:1 pet ether:EtOAc) to give the diacetate (1e) (95 %, 165 mg). IR  $\nu_{\text{max}}$ : 2123, 1739, 1694, 1632  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 1.80–1.97 (m, 2H, 2H-2), 2.04 (s, 6H, OAc), 3.63 (s, 3H, OMe), 3.69–3.90 (m, 2H, 2H-1), 3.83 (s, 3H, OMe), 4.02 (dd, 1H,  $J = 6.2, 12.0$  Hz, H-4), 4.23 (dd, 1H,  $J = 3.6, 12.0$  Hz, H-4'), 4.98–5.17 (m, 1H, H-3), 6.91 (d, 2H,  $J = 9.0$  Hz, ArH), 7.11 (d, 2H,  $J = 9.0$  Hz, ArH). HRMS: calcd for  $\text{C}_{19}\text{H}_{23}\text{N}_3\text{O}_8$  421.1485, found 421.1475.

**General Procedure for Rh(II)-Catalyzed C-H Insertion Reaction.** The Rh(II) catalyst (5 mol %, predried at 110 °C at 0.5 Torr) was suspended in either dry  $\text{CH}_2\text{Cl}_2$ ,  $\text{ClCH}_2\text{CH}_2\text{Cl}$  or  $\text{C}_6\text{H}_6$  (20 mL). A solution of the diazo compound (100 mg) in the same solvent (9 mL) was added, *via* cannula to the above suspension and the reaction was stirred at the specified temperature (see Table 1). When the reaction was complete, as judged by TLC, the reaction mixture was evaporated and the residue was purified.

**4-[(*S*)-1,2-Dihydroxy-1,2-*O*-isopropylidene]ethyl]-3-carbomethoxy-1-(4-methoxyphenyl)-2-pyrrolidinone (5a).** Mixture of diastereomers, 36%. IR  $\nu_{\text{max}}$ : 1742, 1695  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  1.35 (s, 3H, Me), 1.43 (s, 3H, Me), 2.91–3.10 (m, 1H, H-4), 3.33–4.30 (m, 6H, H-3, 2H-5, H-1', H-2'), 3.80 (s, 3H, OMe), 3.83 (s, 3H, OMe), 6.89 (d, 2H,  $J = 9.0$  Hz, Ar H), 7.52 (d, 2H,  $J = 9.0$  Hz, Ar H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  25.1, 26.6, 38.6, 49.1, 52.5, 53.0, 55.5, 67.2, 114.1, 121.9, 132.6, 152.4, 169.8. Anal. Calcd for  $\text{C}_{18}\text{H}_{23}\text{NO}_6$ : C, 61.88; H, 6.64; N, 4.01. Found: C, 62.00; H, 6.79; N, 3.97.

**3-Carbomethoxy-1-(4-methoxyphenyl)-4-[(*S*)-2-oxiranyl]-2-pyrrolidinone (5c).** 4.8:1 mixture of trans<sup>1a,7</sup> diastereomers based on integration of H-3 doublet, 28%. IR  $\nu_{\text{max}}$ : 1742, 1696, 1610, 1585, 1513  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$ : 2.37–2.46 (m, 0.3H, H-4), [2.52 (dd,  $J = 4, 1.6$  Hz)] and 2.57 (dd,  $J = 4.8, 2$  Hz) (H-3')(1H), [2.68 ("t",  $J = 4.2$  Hz)] and 2.80 ("t",  $J = 4$  Hz) (H-3')(1H), 2.76–2.90 (m, 0.7H, H-4), 2.98–3.14 (m, 1H, H-2'), [3.44 (d,  $J = 7.2$  Hz)] and 3.51 (d,  $J = 8$  Hz)(H-3)(1H), 3.58–3.95 (m, 2H, 2H-5), 3.75 (s, 3H, OMe), 3.80 (s, 3H, OMe), 6.82 (d, 2H,  $J = 7.2$  Hz, ArH), 7.40 (d, 2H,  $J = 7.2$  Hz, ArH). HRMS calcd for  $\text{C}_{15}\text{H}_{17}\text{NO}_5$  291.1107, found 291.1117.

**3-Carbomethoxy-1-(4-methoxyphenyl)-4-[(S)-2-oxo-dioxolanyl]-2-pyrrolidinone (5d)** and **3-Carbomethoxy-1-(4-methoxyphenyl)-4-[(S)-2-oxo-dioxolanyl]methyl]-2-azetidinone (6d)**. Obtained as an 1:5.2 ratio of inseparable mixture of **5d:6d** in a combined yield of 60%. Product ratio determined by integration of the  $\gamma$ -lactam H-3 doublet centred at  $\delta$  3.49 and the  $\beta$ -lactam doublets, one centred at  $\delta$  3.98 and the other at 4.02. IR  $\nu_{\max}$ : 1812, 1762, 1735, 1700, 1615, 1513  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ), signals of minor (**5d**) in brackets:  $\delta$  1.96–2.18 (m, 1H), 2.30–2.65 (m, 1H), [3.49 (d,  $J = 8$  Hz,  $\gamma$ -lactam H-3)], 3.80, 3.82, 3.84 (s, 6H, OMe), [3.98 (d,  $J = 2.5$  Hz)] and 4.02 (d,  $J = 2.5$  Hz) (1H,  $\beta$ -lactam H-3), 4.0–4.38 (m, 1H, CHOC(=O)), 4.5–4.67 (m, 2H, CHOC(=O) and  $\beta$ -lactam H-4), 4.76–4.95 (m, 1H, CHOC(=O)), 6.88 (d, 2H,  $J = 7.2$  Hz, ArH), 7.26 (d, 2H,  $J = 7.2$  Hz, ArH). HRMS calcd for  $\text{C}_{16}\text{H}_{17}\text{NO}_7$  355.1005, found 335.1009.

**4-[(S)-2,3-Dihydroxy-2,3-O-isopropylidene]propyl]-3-carbomethoxy-1-(4-methoxyphenyl)-2-azetidinone (6a)**. Mixture of trans<sup>7,10</sup> diastereomers, 37%. IR  $\nu_{\max}$ : 1759, 1732  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  1.33 (s, 3H, Me), 1.43 (s, 3H, Me), 1.68–2.01 (m, 1H, H-1'), 2.22–2.38 (m, 1H, H-1'), [3.35–3.46 (m)], 3.48–3.61 (m, 1H, H-3), 3.79 (s, 3H, OMe), 3.82 (s, 3H, OMe), 3.96–4.30 (m, 3H, H-4, H-4', H-5'), [4.42–4.48 (m)], 4.48–4.59 (m, 1H, H-5'), 6.83–6.94 (m, 2H, Ar H), 7.25–7.38 (m, 2H, Ar H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 25.6, 26.9, 34.1, [36.0], [51.4], 52.5, 52.8, [53.3], 55.5, [56.0], 59.2, [60.2], 69.2, [69.4], 71.9, [73.0], 109.6, [114.5], 114.6, 118.9, [119.2], 130.1, 156.6, 158.5, 167.2. Anal. Calcd for  $\text{C}_{18}\text{H}_{23}\text{NO}_6$ : C, 61.88; H, 6.64; N, 4.01. Found: C, 61.65; H, 6.72; N, 4.13.

**3-Carbomethoxy-1-(4-methoxyphenyl)-4-[(S)-2-oxiranyl]ethyl]-2-azetidinone (6c)**. 1:1 Mixture of trans-diastereomers based on integration of H-3 doublet, 34%. IR  $\nu_{\max}$ : 1754, 1732, 1611, 1585, 1513  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR,  $\delta$ : 1.60 (ddd, 0.7H,  $J = 16.5, 8.4, 8$  Hz, CH") and 2.37–2.50 (m, 1.3H, CH", H-3"), 1.99 (ddd,  $J = 14.8, 9.3, 3.1$  Hz, CH") and 2.18 (ddd,  $J = 14.8, 7.8, 3.7$  Hz, CH")(1H), 2.70 ("t",  $J = 4.1$  Hz) and 2.74 ("t",  $J = 4.1$  Hz) (H-3")(1H), 2.27–3.00 (m, 1H, H-2"), 3.75 (s, 3H, OMe), 3.80 (s, 3H, OMe), 3.94 (d,  $J = 2.3$  Hz) and 4.06 (d,  $J = 2.1$  Hz) (H-3)(1H), 4.42–4.52 (m, 1H, H-4), 6.82 (d, 2H,  $J = 7.2$  Hz, ArH), 7.25 (d, 2H,  $J = 7.2$  Hz, ArH).  $^{13}\text{C}$  NMR,  $\delta$ : 33.2, [34.8], 45.8, [46.6], 47.8, [48.6], 52.5 [52.8], 55.4, 58.6 [59.1], 114.2, [114.5], 118.8, [119.1], 129.9, 156.6, 158.1, [158.2], 167.0, [167.1]. HRMS calcd for  $\text{C}_{15}\text{H}_{17}\text{NO}_5$  291.1107, found 291.1117.

**4-[(S)-2,3-Diacetoxypentyl]-3-carbomethoxy-1-(4-methoxyphenyl)-2-azetidinone (6e)**. Yield: 48%. IR  $\nu_{\max}$ : 1766, 1756, 1612  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  1.73–1.98 (m, 1H, H-1'), 2.07 (s, 3H, OAc), 2.10 (s, 3H, OAc), 2.31–2.60 (m, 1H, H-1'), 3.80 (s, 6H, OMe), 3.93 (dd, 1H,  $J = 13.0, 2.5$  Hz, H-3'), 4.07 (dd, 1H,  $J = 13.0, 2.5$  Hz, H-3'), 4.20–4.50 (m, 2H, H-3, H-2'), 5.11–5.31 (m, 1H, H-4), 6.90 (d, 2H,  $J = 8.9$  Hz, ArH), 7.22–7.34 (m, 2H, ArH).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  20.7, [20.9], 29.7, 32.3, 51.8, 52.9, 55.5, 59.4,

[60.0], 64.5, 64.6, 68.2, [69.0], 114.6, 119.0, [119.2], 123.3, 129.8, 156.7, 166.9, 170.1, 170.5. HRMS: calcd for C<sub>19</sub>H<sub>23</sub>NO<sub>8</sub> 393.1424, found 393.1427.

**1-[(S)-3,4-Dihydroxy-3,4-O-isopropylidene]butyl]-5-methoxy-2-indolinone (7a).** Yield: 17%. IR  $\nu_{\max}$ : 1704, 1600 cm<sup>-1</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  1.34 (s, 3H, Me), 1.42 (s, 3H, Me), 1.90 ("q", 2H, *J* = 6.2 Hz, 2H-2'), 3.50 (s, 2H, H-3), 3.54 (dd, 1H, *J* = 7.3, 6.3 Hz, H-1'), 3.66-3.93 (m, 2H, H-1', H-4'), 3.79 (s, 3H, OMe), 4.00-4.20 (m, 2H, H-3', H-4'), 6.74-6.91 (m, 3H, ArH). Anal. Calcd for C<sub>16</sub>H<sub>21</sub>NO<sub>4</sub>: C, 65.96; H, 7.27; N, 4.81. Found: C, 65.86; H, 7.20; N, 4.83.

**N-[2-((S)-4-(2-Oxo-1,3-dioxolanyl)ethyl)-5-methoxy-2-indolinone (7d).** Yield: 97%. IR  $\nu_{\max}$ : 1798, 1748, 1704, 1644, 1601 cm<sup>-1</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  2.02-2.24 (m, 2H, 2H-2'), 3.51 (s, 2H, 2H-3), 3.60-4.00 (m, 2H, 2H-1''), 3.78 (s, 3H, OMe), 4.11 (dd, 1H, *J* = 8.6, 7.1 Hz, H-5''), 4.57 (t, 1H, *J* = 8.6 Hz, H-5''), 4.65-4.86 (m, 1H, H-4''), 6.73-7.02 (m, 3H, ArH). <sup>13</sup>C NMR (CDCl<sub>3</sub>):  $\delta$ : 32.1, 36.0, 36.1, 55.9, 69.1, 74.8, 108.4, 112.3, 125.8, 137.1, 154.7, 156.1. HRMS calcd for C<sub>14</sub>H<sub>15</sub>NO<sub>5</sub> 277.0950, found 277.0948.

**N-[(S)-3,4-Diacetoxybutyl]-5-methoxy-2-indolinone (7e).** Yield: 20%. IR  $\nu_{\max}$ : 1744, 1707, 1601 cm<sup>-1</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  1.92-2.06 (m, 2H, 2H-2'), 2.05 (s, 3H, OAc), 2.08 (s, 3H, OAc), 3.49 (s, 2H, H-3), 3.58-3.96 (m, 2H, 2H-1'), 3.79 (s, 3H, OMe), 4.09 (dd, 1H, *J* = 12.1, 5.7 Hz, H-4'), 4.27 (dd, 1H, *J* = 12.1, 3.8 Hz, H-4'), 4.99-5.16 (m, 1H, H-3'), 6.63-7.00 (m, 3H, ArH). <sup>13</sup>C NMR (CDCl<sub>3</sub>):  $\delta$ : 20.7, 21.0, 28.2, 36.1, 36.2, 55.8, 64.6, 69.2, 108.2, 112.1, 112.1, 126.0, 126.1, 128.2, 133.6, 156.9, 170.5. CI-LRMS (NH<sub>3</sub>, *m/z*, %): 353 (M + NH<sub>4</sub><sup>+</sup> 14), 336 (M+1, 100), 296 (M-AcOH, 93). HRMS calcd for C<sub>17</sub>H<sub>21</sub>NO<sub>6</sub> 335.1383, found 335.1379.

**4-[(S)-1,2-Dihydroxy-1,2-O-isopropylidene]ethyl]-1-(4-methoxyphenyl)-2-pyrrolidinone (8).** The  $\gamma$ -lactam (5a) (102 mg, 0.290 mmol) was dissolved in 10:1 DMSO:H<sub>2</sub>O (7.5 mL) and powdered NaCl (53.2 mg, 0.910 mmol) was added. The solution was stirred at 110 °C for 28 h then cooled to rt. Et<sub>2</sub>O (25 mL) and H<sub>2</sub>O (17 mL) were added and the organic layer was separated. The aqueous layer was extracted with Et<sub>2</sub>O (5 x 20 mL) and the combined ethereal layers were washed with brine (3 x 15 mL), dried, filtered and concentrated. After purification (20:1 CH<sub>2</sub>Cl<sub>2</sub>:acetone) the  $\gamma$ -lactam (8) (77.9 mg, 92%) was obtained as a mixture of diastereomers. IR  $\nu_{\max}$ : 1694 cm<sup>-1</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$ : 1.37 (s, 3H, Me), 1.42 (s, 3H, Me), 2.20-2.76 (m, 3H, H-3, H-4), 3.58-3.72 (m, 1H, H-2'), 3.79 (s, 3H, OMe), 3.76-4.20 (m, 4H, H-5, H-1', H-2'), 6.89 (d, 2H, *J* = 9.1 Hz, Ar H), 7.51 (d, 2H, *J* = 9.1 Hz, Ar H). <sup>13</sup>C NMR (CDCl<sub>3</sub>):  $\delta$ : 25.3, [26.6], 26.8, [33.8], [34.2], 35.1, 51.5, [55.4], 55.5, 67.8, 77.7, 109.6, 114.1, 121.8, [121.9], 132.3, 156.7, 172.1. Anal. Calcd for C<sub>16</sub>H<sub>21</sub>NO<sub>4</sub>: C, 65.96; H, 7.27; N, 4.81. Found: C, 65.89; H, 7.20; N, 4.88.

**4-[(S)-2-Benzoyloxy-1-hydroxy]ethyl]-1-(4-methoxyphenyl)-2-pyrrolidinone (9b).** The ketal (8) (123 mg, 0.42 mmol) was dissolved in a mixture of MeOH:1M aqueous HCl (10:1 v/v, 5 mL) and stirred at rt for 24 h. The solvent was evaporated and the residue was taken into CH<sub>2</sub>Cl<sub>2</sub> (25 mL) and dried with a 1:1

mixture anhydrous Na<sub>2</sub>SO<sub>4</sub> and anhydrous K<sub>2</sub>CO<sub>3</sub>. The solution was filtered, and evaporated to give the crude diol (**9a**) (75 mg, 71 %). <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 2.30–2.70 (m, 3H, H-3, H-4), 3.00–3.11 (br s, 1H, OH), 3.40–3.90 (m, 6H, H-5, CH<sub>2</sub>O, CHO, OH), 3.80 (s, 3H, OMe), 6.90 (d, 2H, J = 7.2 Hz, ArH), 7.45 (d, 2H, J = 7.2 Hz, ArH). Compound (**9a**) was used in the next step without further purification.

The diol (**9a**) (75 mg, 0.298 mmol) was dissolved in dry CH<sub>2</sub>Cl<sub>2</sub> (1.5 mL) containing dry pyridine (0.5 mL). The solution was cooled to 0 °C and was treated, dropwise, with benzoyl chloride (36 uL, 0.313 mmol). The mixture was stirred at 0 °C and allowed to warm slowly to rt (18 h). The mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub> (5 mL), washed successively with water (5 mL), saturated CuSO<sub>4</sub> solution (2 x 5 mL), water, saturated NaHCO<sub>3</sub> and dried. The filtered solution was evaporated and the oily residue purified (pet. ether-EtOAc, 1:1) to give 103 mg (97%) of monobenzoate (**9b**). IR ν<sub>max</sub>: 3600–3189, 1718, 1672, 1513 cm<sup>-1</sup>. <sup>1</sup>H NMR, δ: 2.40–2.72 (m, 3H, 2H-3, H-4), 3.72 (s, 3H, OMe), 3.76–4.00 (m, 3H, 2H-5, OH), 4.20–4.47 (m, 1H, H-1'), 4.26 (dd, 1H, J = 11.4, 5.7 Hz, H-2'), 4.40 (dd, 1H, J = 11.4, 4.3 Hz, H-2'), 6.82 (d, 2H, J = 7.2 Hz, ArH), 7.3–7.6 (m, 5H, ArH, PhH), 8.0 (d, 2H, J = 7 Hz, PhH). <sup>13</sup>C NMR, δ: 34.1, 35.2 (-), 51 (-), 55.3, 67.2 (-), 71, 113.8, 122, 128.1, 128.3, 129.3, 129.5, 129.7, 131.9, 133.2, 156.6, 166.7, 172.8. HRMS calcd for C<sub>20</sub>H<sub>21</sub>NO<sub>5</sub> 355.1420, found 355.1423.

**4-[(2-Benzoyloxy)ethyl]-1-(4-methoxyphenyl)-2-pyrrolidinone (10b)**. The monobenzoate (**9b**) (102 mg, 0.287 mmol) was dissolved in dry (CH<sub>2</sub>Cl)<sub>2</sub> (8 mL). 1,1'-Thiocarbonyldiimidazole (128 mg, 0.718 mmol) was added and the mixture was refluxed for 2.5 d. Then the mixture was cooled to rt and the solvent was removed on the rotary evaporator. The residual oil was taken into CH<sub>2</sub>Cl<sub>2</sub> (10 mL) and the organic phase was washed with aqueous 1M HCl (2 x 5 mL), water (5 mL), saturated NaHCO<sub>3</sub> (5 mL), dried and filtered. The filtrate was evaporated to leave a yellow residue, which after purification (CH<sub>2</sub>Cl<sub>2</sub>-acetone, 10:1) gave the thioimidazolide (**10a**) (115 mg, 86%). IR ν<sub>max</sub>: 1723, 1693, 1601, 1512, 1391, 1230, 1178 cm<sup>-1</sup>. <sup>1</sup>H NMR, δ: [2.53 (dd, J = 15.9, 8.8 Hz)] and 2.56 (dd, J = 16.8, 8.8 Hz) H-3(1H), 2.82 (dd, 1H, J = 16.8, 8.8 Hz, H-3), 2.90–3.25 (m, 1H, H-4), 3.79 (dd, 1H, J = 10.6, 7 Hz, H-5), 3.93 ("t", 1H, J = 8.8 Hz, H-5), 4.55 (dd, 1H, J = 12.4, 5.3 Hz, H-2'), 4.80 (dd, J = 12.4, 3.2 Hz) and [4.96 (dd, J = 12.4, 3.3 Hz)(H-2')(1H), [5.62–5.74, (m)] and 6.02–6.18 (m) (H-1')(1H), 6.85 (d, 2H, J = 8 Hz, ArH), 7.05 (br s, 1H, imidazole-H), 7.33–7.65 (m, 6H, ArH, PhH, imidazole-H), 7.96 (d, 2H, J = 7.0 Hz, PhH), 8.32 (br s, 1H, imidazole-H).

A solution of the **10a** (115 mg, 0.247 mmol) and AIBN (8.1 mg, 0.049 mmol) in dry toluene (2 mL) was added *via* cannula to a solution of *n*-Bu<sub>3</sub>SnH (106 uL, 0.395 mmol) in dry toluene (5 mL) at reflux. The mixture was stirred at reflux for 2.45 h and then cooled to rt. the reaction mixture was evaporated and the oily residue was taken into ether (10 mL). Aqueous 10% KF (5 mL) was added and the biphasic mixture was stirred at rt for 1 h. The ethereal layer was separated and the aqueous phase was extracted with ether.

(2 x 10 mL). The combined ether phases were washed with brine (2 x 10 mL), dried, filtered and evaporated. The residue was purified (pet. ether-EtOAc, 2:1 and then 1:1) to provide 68 mg (82%) of **10b**. IR  $\nu_{\text{max}}$ : 1716, 1692, 1601, 1589, 1512  $\text{cm}^{-1}$ .  $^1\text{H NMR}$ ,  $\delta$ : 1.94 ("q" 2H,  $J = 6.8$  Hz, 2H-1'), 2.30 (dd, 1H,  $J = 15.5, 7.7$  Hz, H-3), 2.50–2.60 (m, 1H, H-4), 2.63 (dd, 1H,  $J = 15.5, 8.2$  Hz, H-3), 3.50 (dd, 1H,  $J = 9.7, 7.1$  Hz, H-5), 3.62 (s, 3H, OMe), 3.88 (dd, 1H,  $J = 9.7, 7.7$  Hz, H-5), 4.25–4.45 (m, 2H, 2H-2'), 6.80 (d, 2H,  $J = 7.2$  Hz, ArH), 7.30–7.60 (m, 5H, ArH, PhH) 8.00 (d, 2H,  $J = 7$  Hz, PhH),  $^{13}\text{C NMR}$ ,  $\delta$ : 29.1, 33.1, 38.8, 54.4, 62.8, 113.8, 121.6, 128.3, 129.3, 129.7, 132.2, 133.0, 156.4, 166.3, 172.6. HRMS calcd for  $\text{C}_{20}\text{H}_{21}\text{NO}_4$  339.1471, found 339.1469.

**(R)-3-(1-Carbobenzyloxypyrrolidinyl)acetic acid (12)**. The benzoate (**10b**) (64 mg, 0.188 mmol) was dissolved in MeCN (3 mL) and the solution was cooled to 0 °C. A solution of CAN (331 mg, 0.604 mmol) in distilled water (1.5 mL) was added dropwise. After addition was complete, the reaction mixture was stirred for 20 min at 0 °C. Then aqueous 10%  $\text{NaHSO}_3$  (1 mL) and saturated  $\text{NaHCO}_3$  (1 mL) were added and the mixture was stirred at rt for 1 h. Ethyl acetate (5 mL) was added and the mixture was filtered through Celite. The residue was washed with EtOAc (2 x 5 mL) and the combined filtrates were evaporated. The crude product was taken into  $\text{CH}_2\text{Cl}_2$  and anhydrous  $\text{Na}_2\text{SO}_4$  was added. The  $\text{CH}_2\text{Cl}_2$  solution was filtered, evaporated and the crude residue was purified: elution with 1:1 pet. ether-EtOAc, furnished the unexpected 4-[(2-benzyloxy)ethyl]-1-(4-hydroxyphenyl)-2-pyrrolidinone (10 mg, 16%). IR  $\nu_{\text{max}}$ : 3542–3095, 3060, 1714, 1678, 1600, 1514  $\text{cm}^{-1}$ .  $^1\text{H NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  1.95 ("q", 2H,  $J = 7.7$  Hz, 2H-1'), 2.12 (dd, 1H  $J = 16, 8$  Hz, H-3), 2.50–2.80 (m, 1H, H-4), 2.75 (dd, 1H,  $J = 16, 8$  Hz, H-3), 3.52 (dd, 1H,  $J = 9.6, 6.4$  Hz, H-5), 3.88 (dd, 1H,  $J = 9.6, 8$  Hz, H-5), 4.26–4.45 (m, 2H, 2H-2'), 6.70 (d, 2H,  $J = 7.2$  Hz, ArH), 7.25 (d, 2H,  $J = 7.2$  Hz, ArH), 7.35–7.60 (m, 3H, PhH), 8.00 (d, 2H,  $J = 7$  Hz, PhH).

Further elution with 4:1  $\text{CH}_2\text{Cl}_2$ -acetone provided the desired product (**11a**) (35 mg, 81%). IR  $\nu_{\text{max}}$ : 3631–3036, 1715, 1691, 1601  $\text{cm}^{-1}$ .  $^1\text{H NMR}$ ,  $\delta$ : 1.92 ("q", 2H,  $J = 6.5$  Hz, 2H-1'), 2.09 (dd, 1H,  $J = 16.8, 8$  Hz, H-3), 2.50 (dd, 1H,  $J = 16.8, 8.8$  Hz, H-3), 2.50–2.70 (m, 1H, H-4), 3.10 (dd, 1H,  $J = 9.3, 7.2$  Hz, H-5), 3.56 (dd, 1H,  $J = 9.3, 8$  Hz, H-5), 4.25–4.40 (m, 2H, 2H-2'), 6.75 (br s, 1H, NH), 7.35–7.60 (m, 3H, PhH), 8.0 (d, 2H,  $J = 7$  Hz, PhH).

A solution of the benzoate (**11a**) (35 mg, 0.15 mmol) in dry THF (2 mL) was transferred *via* cannula to a suspension of  $\text{LiAlH}_4$  (40 mg, 1.05 mmol) in dry THF (3 mL). The mixture was refluxed for 18 h, then cooled to 0 °C and aqueous 1M NaOH (1 mL) was carefully added. Brine (2 mL) and excess solid NaCl were added and the mixture was stirred at rt for 45 min. The biphasic mixture was recooled to 0 °C and excess benzyl chloroformate (50  $\mu\text{L}$ ) was added and the mixture was stirred at 0 °C for 5 h. Ethyl acetate (10 mL) was added to the mixture and the aqueous phase was separated and back-extracted with more EtOAc (2 x 5 mL). The combined organic phases were washed with brine (5 mL), dried, filtered and

evaporated. Purification of the crude product (4:1 CH<sub>2</sub>Cl<sub>2</sub>-acetone) yielded 17 mg (66%) of **11b**. IR  $\nu_{\max}$ : 3636–3189, 3063, 3034, 1694 cm<sup>-1</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$ : 1.35–1.52 (m, 1H, H-4), 1.49 (“q”, 2H,  $J = 7.5$  Hz, 2H-1’), 1.90–2.03 (m, 2H, H-4, OH), 2.03–2.32 (m, 1H, H-3), 2.90 (dd, 1H,  $J = 10.8, 9.1$  Hz, H-2), 3.25 (ddd, 1H,  $J = 10.9, 10.9, 5.8$  Hz, H-5), 3.47 (dtd, 1H,  $J = 10.9, 8.6, 3.3$  Hz, H-5), 3.57 (dd, 1H,  $J = 10.8, 7$  Hz, H-2), 3.60 (“t”, 2H,  $J = 6.1$  Hz, 2H-2’), 5.10 (s, 2H, CH<sub>2</sub>Ph), 7.30 (s, 5H, PhH).

The primary alcohol (**11b**) (16 mg) was dissolved in reagent grade acetone and was cooled to 0 °C. Jones’ reagent was added dropwise to the mixture until the orange-red color persisted for at least 5 min. 2-Propanol (0.1 mL) was added to destroy excess oxidant and then Celite was added. The mixture was stirred for 30 min and then was filtered through Celite. The residue was washed with EtOAc (3 x 10 mL) and the combined filtrates were evaporated. The residual oil was purified (CH<sub>2</sub>Cl<sub>2</sub>-acetone, 4:1) to afford 15 mg (88%) of the acid (**12**). IR  $\nu_{\max}$ : 3518–2531, 3054, 1700, 1675 cm<sup>-1</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  1.46–1.70 (m, 1H, H-4), 2.00–2.2 (m, 1H, H-4), 2.43 (dd, 2H,  $J = 7.9, 1.9$  Hz, CH<sub>2</sub>CO<sub>2</sub>), 2.46–2.65 (m, 1H, H-3), 3.03 (dd, 1H,  $J = 10.9, 7.6$  Hz, H-2), 3.30–3.43 (m, 1H, H-5), 3.47–3.60 (m, 1H, H-5), 3.70 (dd, 1H,  $J = 10.9, 7.6$  Hz, H-2), 5.10 (s, 2H, CH<sub>2</sub>Ph), 7.35 (s, 5H, PhH), 7.62–8.50 (br hump, 1H, CO<sub>2</sub>H). <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$ : 30.7, 37.1, 45.4, 51.1, 66.8, 127.9, 128.4, 136.8, 154.9, 176.9. HRMS calcd for C<sub>14</sub>H<sub>17</sub>NO<sub>4</sub> 263.1158, found 256.1162.

**4-[(1S)-1-Hydroxybutyl]-1-(4-methoxyphenyl)-2-pyrrolidinone (15)**. A stock solution of CHCl<sub>3</sub> (5 mL), pyridine (2.5 mL, 33.2 mmol) and *i*-Pr<sub>2</sub>EtN (24  $\mu$ L, 0.25 mmol) was prepared. The diol (**9a**) (54.2 mg, 0.220 mmol) was dissolved in 3 mL of the above solution. The diol solution was cooled to 0 °C and MeSO<sub>2</sub>Cl (20  $\mu$ L, 0.26 mmol) in CHCl<sub>3</sub> (1 mL) was added *via* cannula. The reaction mixture was stirred at 0 °C for 15 min and then raised to rt. After 17 h the solvent was removed *in vacuo* and the residue was purified (4:1 then 1:1 CH<sub>2</sub>Cl<sub>2</sub>:acetone) to give the mesylate (**13**) (98 %, 70 mg). IR  $\nu_{\max}$ : 3648-3095, 1697, 1667 cm<sup>-1</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  2.35–2.75 (m, 3H, 2H-3, H-4), 3.06 (s, 3H, MeSO<sub>2</sub>), 3.77 (s, 3H, OMe), 3.80–3.95 (m, 4H, 2H-5, H-1’, OH), 4.15 (dd, 1H,  $J = 10.7, 6.2$  Hz, H-2’), 4.28 (dd, 1H,  $J = 10.8, 3.2$  Hz, H-2’), 6.87 (d, 2H,  $J = 8.9$  Hz, Ar H), 7.44 (d, 2H,  $J = 8.9$  Hz, Ar H).

The mesylate (**13**) (22.0 mg, 0.068 mmol) was dissolved in THF (3 mL) and cooled to 0 °C in an ice-water bath. After stirring for 20 min at 0 °C KOBu-*t* (8.56 mg, 0.076 mmol) was added quickly, and the mixture was warmed slowly to rt and stirred for 24 h. The reaction was quenched by addition of saturated aqueous NH<sub>4</sub>Cl (0.5 mL), and THF was removed *in vacuo*. The residue was taken into CH<sub>2</sub>Cl<sub>2</sub> (10 mL) and washed with brine (3 x 10 mL). The organic layer was dried, filtered, concentrated and then purified (4:1 CH<sub>2</sub>Cl<sub>2</sub>:acetone) to give the epoxide (**14**) (78 %, 12.41 mg). IR  $\nu_{\max}$ : 1694 cm<sup>-1</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  2.20–2.90 (m, 5H, 2H-3, H-4, 2H-3’), 3.02–3.12 (m, 1H, H-1’), 3.72–3.84 (m, 1H, H-5), 3.79 (s, 3H,



OMe), 3.87–4.02 (m, 1H, H-5), 6.90 (d, 2H,  $J = 9.0$  Hz, ArH), 7.48 (d, 2H,  $J = 9.0$  Hz, ArH).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  33.7, 34.9, 46.1, 51.5, 53.5, 55.5, 114.1, 121.9, 132.1, 156.8, 172.0.

$\text{CuBr}\cdot\text{SMe}_2$  (67.4 mg, 0.33 mmol) was suspended in  $\text{Et}_2\text{O}$  (7 mL), then cooled to  $-78$  °C and 1.8M  $\text{EtLi}$  (0.55 mL, prepared from 1.90 g lithium metal and 9.32 mL  $\text{EtBr}$ ) in  $\text{Et}_2\text{O}$  was added slowly to give a yellow solution of lithium diethylcuprate. A solution of **14** (15.6 mg, 0.067 mmol) in  $\text{Et}_2\text{O}$  (2.5 mL) was added to the cuprate solution *via* cannula. The red solution was stirred for 45 min at  $-78$  °C then warmed to  $-35$  °C ( $\text{MeCN}$ /dry ice) which after 10 min the red colour changed to dark purple. After 1 h saturated aqueous  $\text{NH}_4\text{Cl}$  (3 mL) was added to the reaction mixture and it was warmed to rt. The mixture was separated and the aqueous layer was washed with  $\text{Et}_2\text{O}$  (4 x 20 mL). The combined organic layers were dried, filtered, concentrated and purified (8:1  $\text{CH}_2\text{Cl}_2$ :acetone) to give the alcohol (**15**) (85 %, 23.6 mg).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  0.97 (t, 3H  $J = 6.5$  Hz,  $\text{CH}_3$ ), 1.12–1.77 (m, 5H, H-4, 2H-2', 2H-3'), 2.35–2.75 (m, 3H, 2H-3, H-1'), 3.57–3.72 (br. s, 1H, OH), 3.79 (s, 3H, OMe), 3.76–3.94 (m, 2H, H-5), 6.89 (d, 2H,  $J = 9.1$  Hz, Ar H), 7.50 (d, 2H,  $J = 9.1$  Hz, Ar H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  14.0, 18.7, 35.7, 37.3, 37.7, 51.2, 55.5, 73.4, 114.0, 121.0, 132.8, 156.6, 172.8.

**4-Butyl-1-(4-methoxyphenyl)-2-pyrrolidinone (16)**. The alcohol (**15**) (7.55 mg, 0.0290 mmol) and DMAP (14.2 mg, 0.117 mmol) were dissolved in  $\text{MeCN}$  (1 mL), and stirred for 10 min. Phenyl chlorothioformate (0.1 mL, 0.723 mmol) was added to the reaction mixture and the reaction mixture was stirred for 47 h. The solvent was evaporated and the residue was purified (4:1  $\text{CH}_2\text{Cl}_2$ :acetone) to give the corresponding thionocarbonate derivative (5.59 mg, 49 %).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$ : 1.00 (t, 3H,  $J = 7.1$  Hz, Me), 1.40–2.00 (m, 4H, 2H-2', 2H-3'), 2.53 (dd, 1H,  $J = 17.4, 8.7$  Hz, H-3), 2.72 (dd, 1H,  $J = 17.4, 9.1$  Hz, H-3), 2.85–3.00 (m, 1H, H-4), 3.80 (s, 3H, OMe), 3.75–4.00 (m, 2H, H-5), 5.55–5.75 (m, 1H, H-1'), 6.80–7.50 (m, 9H, PhH, ArH). The thionocarbonate (5.59 mg, 0.014 mmol) and AIBN (1.8 mg, 0.11 mmol) were dissolved in toluene (1.3 mL) and the solution was heated at 80 °C in an oil bath.  $n\text{-Bu}_3\text{SnH}$  (0.02 mL, 0.074 mmol) was added and the reaction mixture was heated at 80 °C for 24 h. The cooled reaction mixture was diluted with  $\text{Et}_2\text{O}$  (5 mL) and 10% aqueous KF (1 mL) were added. The mixture was stirred for 30 min, the organic phase was separated and the aqueous layer was reextracted with  $\text{CH}_2\text{Cl}_2$  (5 x 10 mL). The combined organic layers were dried, filtered and concentrated. Purification of the residual oil (hexane and then 8:1, 5:1 and finally 3:1 pet ether:EtOAc) gave the known  $\gamma$ -lactam (**16**) (99 %, 3.46 mg).<sup>7</sup> The  $^1\text{H}$  NMR spectrum and TLC ( $R_f$ : 0.29, 2:1 pet ether:EtOAc) were identical to the reference compound [(*S*)-**16**].<sup>1a</sup> HPLC analysis was performed using a Chiralcel<sup>®</sup> OB column (70:30 hexane:2-propanol at 1.5 mL/min, UV ( $\lambda = 254$  nm) detection). Peak area analysis indicated an ee of 74 %. IR  $\nu_{\text{max}}$ : 1691, 1645  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  0.93 (t, 3H,  $J = 7.6$  Hz,  $\text{CH}_3$ ), 1.22–1.60 (m, 6H,

3CH<sub>2</sub>'s), 2.24 (dd, 1H, *J* = 15.9, 7.1 Hz, H-3), 2.40 ("quintet", 1H, *J* = 7.1 Hz, H-4), 2.70 (dd, 1H, *J* = 15.9, 7.1 Hz, H-3), 3.45 (dd, 1H, *J* = 9.6, 6.8 Hz, H-5), 3.82 (s, 3H, OMe), 3.90 (dd, 1H, *J* = 9.6, 9.1 Hz, H-5), 6.88 (d, 2H, *J* = 8.7 Hz, ArH), 7.50(d, 2H, *J* = 8.7 Hz, ArH). <sup>13</sup>C NMR (CDCl<sub>3</sub>): δ 14.0, 22.5, 29.5, 31.5, 34.2, 39.0, 54.9, 55.7, 114.1, 121.7, 132.7, 156.5, 173.4.

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#### REFERENCES AND NOTES

1. (a) A. G. H. Wee, B.-S. Liu, and D. D. McLeod, *J. Org. Chem.*, 1998, **63**, 4218. (b) A. G. H. Wee and B.-S. Liu, *Tetrahedron Lett.*, 1996, **37**, 145.
2. Other related studies: (a) M. Anada and S.-i. Hashimoto, *Tetrahedron Lett.*, 1998, **39**, 79. (b) M. P. Doyle, M. N. Protopopova, W. R. Winchester, and K. L. Daniel, *Tetrahedron Lett.*, 1992, **33**, 7819.
3. (a) D. F. Taber, K. K. You, and A. Rheingold, *J. Am. Chem. Soc.*, 1996, **118**, 547. (b) D. F. Taber and Y. Song, *J. Org. Chem.*, 1996, **61**, 6706. (c) T. Yakura, S. Yamada, A. Ueki, and M. Ikeda, *Synlett*, 1997, 185.
4. S. Saito, T. Hasegawa, M. Inaba, R. Nishida, T. Fujii, S. Nomizu, and T. Moriwake, *Chem. Lett.*, 1984, 1389.
5. B. Neises and W. Steglich, *Angew. Chem., Int. Ed. Engl.*, 1978, **17**, 522.
6. D. F. Taber, R. E. Ruckle, Jr., and M. J. Hennesy, *J. Org. Chem.*, 1986, **51**, 4077.
7. A. G. H. Wee, B.-S. Liu, and L. Zhang, *J. Org. Chem.*, 1992, **57**, 4404.
8. S.-i. Hashimoto, N. Watanabe, M. Anada, and S. Ikegami, *J. Synth. Org. Chem, Jpn.*, 1996, **54**, 114.
9. M. P. Doyle, V. Bagheri, M. M. Pearson, and J. D. Edwards, *Tetrahedron Lett.*, 1989, **30**, 7001.
10. Component A (*R<sub>t</sub>* = 23.6 min), <sup>1</sup>H NMR δ: 1.25 (s, 3H, Me), 1.34 (s, 3H, Me), 1.73 (dt, 1H, *J* = 9.5, 14.1 Hz, CH), 2.25 (dt, 1H, *J* = 3.9, 14.1 Hz, CH'), 3.47 ("t", 1H, *J* = 7.3 Hz, H-3'), 3.73 (s, 6H, OMe), 3.93 (d, 1H, *J* = 2.5 Hz, H-3), 4.01 (dd, 1H, *J* = 7.7, 6.1 Hz, H-3'), 4.07-4.22(m, 1H, H-2'), 4.33-4.48 (m, 1H, H-4), 6.81(d, 2H, *J* = 9.2 Hz, ArH), 7.26 (d, 2H, *J* = 9.2 Hz, ArH). Component B (*R<sub>t</sub>* = 26.6 min), <sup>1</sup>H NMR δ: 1.27 (s, 3H, Me), 1.35 (s, 3H, Me), 1.86 (ddd, 1H, *J* = 14.3, 8.9, 3.5 Hz, CH'), 2.23 (ddd, 1H, *J* = 14.3, 8.4, 2.7 Hz, CH'), 3.48 ("t", 1H, *J* = 7.4 Hz, H-3'), 3.72 (s, 6H, OMe), 3.97 (dd, 1H, *J* = 7.4, 5.9 Hz, H-3'), 4.01 (d, 1H, *J* = 2.2 Hz, H-3), 4.03-4.21 (m, 1H, H-2'),

- 4.47 (dt, 1H,  $J = 2.2, 8.8$  Hz, H-4), 6.81 (d, 2H,  $J = 9.2$  Hz, ArH), 7.22 (d, 2H,  $J = 9.2$  Hz, ArH).
11. (a) K. D. Barrow and T. M. Spotwood, *Tetrahedron Lett.*, 1965, 3325. (b) H. B. Kagan, J. J. Basselier, and J. L. Luche, *Tetrahedron Lett.*, 1964, 941.
  12. J. R. Rasmussen, *J. Org. Chem.*, 1980, **45**, 2725.
  13. J. Eustache, A. Grob, C. Lam, O. Sellier, and G. Schulz, *Bioorg. Med. Chem. Lett.*, 1998, **8**, 2961.
  14. M. J. Robins and P. J. Wilson, *J. Am. Chem. Soc.*, 1981, **103**, 932.
  15. W. C. Still, M. Kahn, and A. Mitra, *J. Org. Chem.*, 1978, **43**, 2923.