Addition reaction of benzylbenzylidenenamine to lithium enolates of 1,3-dioxolan-4-one: synthesis of 2-phenylisoserines

Lizbeth Juárez-Guerra, Susana Rojas-Lima,* and Heraclio López-Ruiz

Área Adémica de Química,Universidad Autónoma del Estado de Hidalgo, Carretera Pachuca-Tulancingo Km. 4.5, Ciudad Universitaria, 42184, Mineral de la Reforma Hidalgo, México
E-mail: lima@uaeh.edu.mx

Abstract

The synthesis of two new 2-phenylisoserines, each bearing a quaternary stereocenter is described. These compounds, which are analogs of the amino acid side chain found in taxol and taxotere, were obtained by addition of the lithium enolates of (2*S*,5*S*)-2-isopropyl-5-phenyl-1,3-dioxolan-4-one and (2*S*,5*S*)-2-*tert*-butyl-2-methyl-5-phenyl-1,3-dioxolan-4-one to benzylbenzylideneamine in the presence of $BF_3{\cdot}O(Et)_2$. The diastereomeric mixtures were separated in each case and the absolute configurations thereof were determined by X-ray analysis.

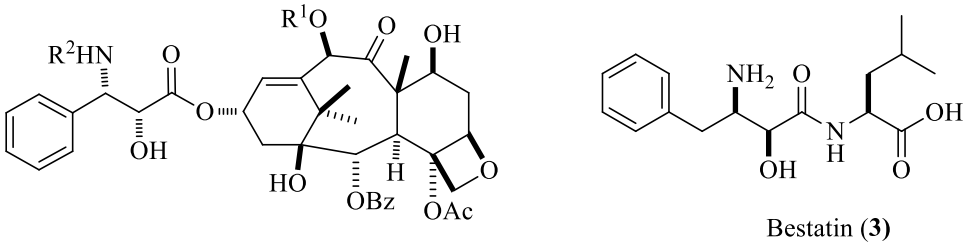
Keywords: 2-Phenylisoserines, 1,3-dioxolan-4-one, Mannich reaction, benzylbenzyliden-enamine

Introduction

The Mannich reaction and transformations involving nucleophilic addition to the C=N of imine derivatives are of significant importance in organic synthesis.[1] Isoserines (α-hydroxy-β-amino acids) are key molecules present in important bioactive substances such as the anticancer agents paclitaxel **1**, docetaxel **2** and bestatin **3** (Figure 1).[2]

Because of their importance, several efficient methods to synthesize isoserines have been developed. Catalytic asymmetric synthesis and especially asymmetric aminohydroxylation have been applied to the synthesis of the analogs of the docetaxel side chain.[3] Recently, Hu reported an efficient synthesis of α-hydroxy-β-aminoesters containing quaternary stereocenters by trapping imines and diazo compound with oxonium ylide generated in situ from rhodium carbenoids and an alcohol.[4] Most notably, certain catalytic Mannich-type reactions have considerable precedent for the preparation of α-hydroxy-β-amino acids derivatives.[5] Bataglia has developed syntheses of chiral α-substituted isoserines, using *cis*/*trans* mixtures of cyclic 1,3-dioxolan-4-one that were not enatiomerically pure.[6] In order to widen the scope of the 1,3-

dioxolan-4-one based lithium enolate methodology it was of interest to study the reaction at low temperature using benzylbenzylideneamine as the electrophile in the presence of Lewis acids.

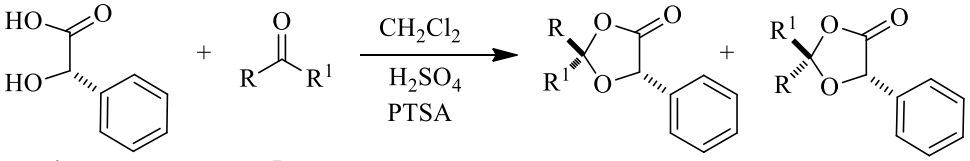


Paclitaxel (Taxol) (**1**) R^1 = Ac, R^2 = Bz
Docetaxel (Taxotere) (**2**) R^1 = H, R^2 = Boc

Figure 1. Structures of paclitaxel, docetaxel and bestatin.

Results and Discussion

Preparation of chiral 1,3-dioxolan-4-ones (6a-b and 8a-b) and configurational assignments
As shown in Scheme 1, the chiral 1,3-dioxolan-4-ones (2*R*,5*S*)-**6a**, (2*S*,5*S*)-**6a**, (2*R*,5*S*)-**6b** and (2*S*,5*S*)-**6b** were prepared from (*S*)-mandelic acid **4** with isobutyraldehyde **5a** or pinacolone **5b** using a slight modification of the known procedure.[7] The reaction of the *S*-mandelic acid **4** with isobutyraldehyde **5a** (Scheme 1), gave a 4:5 diastereomeric mixture of (2*R*,5*S*)-**6a** and (2*S*,5*S*)-**6a**. The ratio of these two diastereomers was determined by ^{1}H NMR spectra data on the crude reaction products. Each diastereomer could be obtained pure by column chromatography.[8] Their structures were assigned by comparison of the chemical shifts of H-2. The analogous reaction of **4** with pinacolone **5b** gave a 6:5 diastereomeric mixture of (2*R*,5*S*)-**6b** and (2*S*,5*S*)-**6b**. The absolute configuration of (2*R*,5*S*)-**6b** and (2*S*,5*S*)-**6b** was further confirmed by X-ray analysis.[9] (Figure 2 and Figure 3).



4 **5**

a: R = H, R^1 = -$CH(CH_3)_2$ (2*R*,5*S*)-**6a** (2*S*,5*S*)-**6a**
b: R = -CH_3, R^1 = -$C(CH_3)_3$ (2*R*,5*S*)-**6b** (2*S*,5*S*)-**6b**

Scheme 1

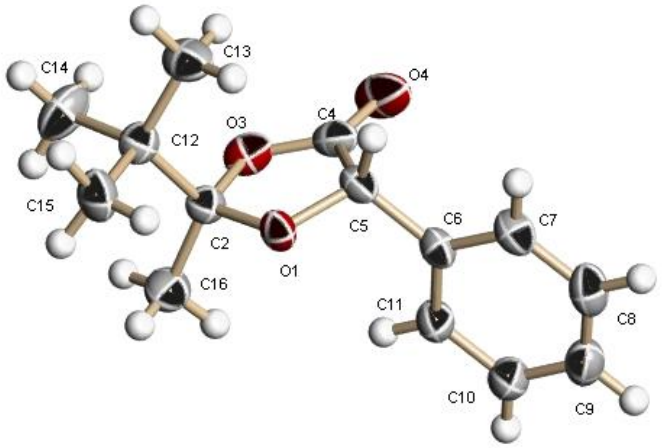


Figure 2. X-ray structure of (2*R*,5*S*)-**6b.**

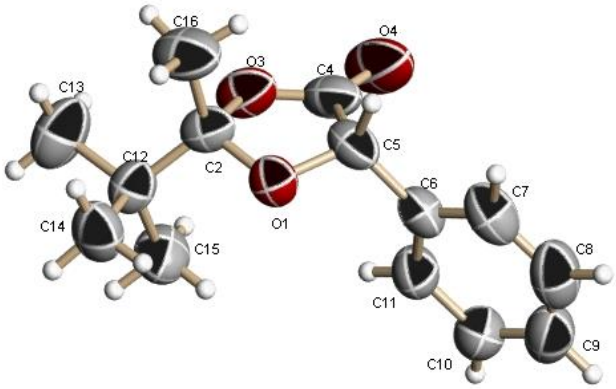
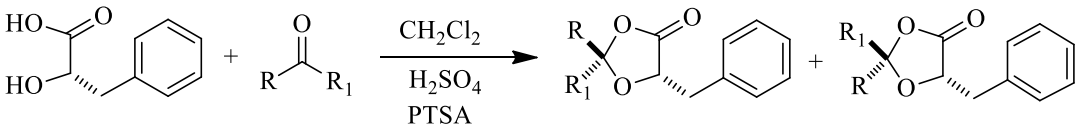


Figure 3. X-ray structure of (2*S*,5*S*)-**6b.**

Isobutyraldehyde **5a** and pinacolone **5b** were also reacted with *S*-phenyllactic acid **7** (Scheme 2). The acid catalyzed reaction of the *S*-phenyllactic acid **7** with isobutyraldehyde (see Experimental Section) gave a 2:1 diastereomeric mixture of (2*R*,5*S*)-**8a** and (2*S*,5*S*)-**8a**. The ratio of these two diastereomers was determined by ^{1}H NMR spectral data on the crude reaction products. The absolute configurations of (2*R*,5*S*)-**8a** and (2*S*,5*S*)-**8a** were further confirmed by Noesy spectra.

S-Phenyllactic acid **7** and pinacolone **5b**, under similar conditions, gave a 2:3 diastereomeric mixture of (2*R*,5*S*)-**8b** and (2*S*,5*S*)-**8b**. The absolute configuration of (2*R*,5*S*)-**8b** was established by X-ray analysis.[9] (Figure 4).



7 5

a: R = H, R1 = -CH(CH$_3$)$_2$ (2R,5S)-8a (2S,5S)-8a

b: R = -CH3, R1 = -C(CH$_3$)$_3$ (2R,5S)-8b (2S,5S)-8b

Scheme 2

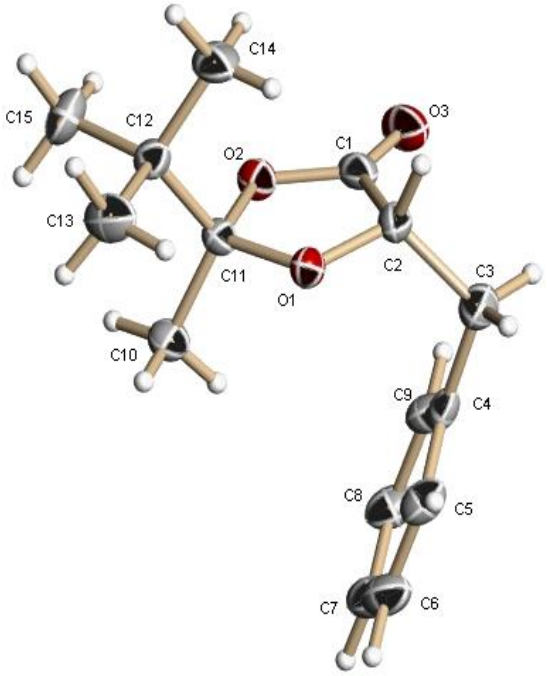
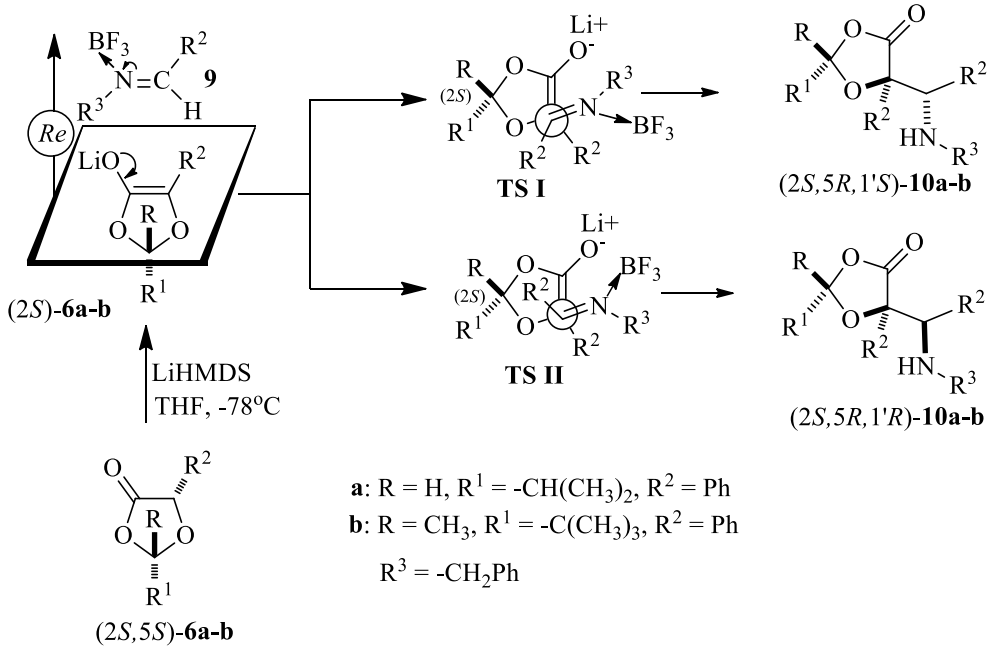


Figure 4. X-ray structure of (2*R*,5*S*)-**8b.**

Reaction of the enolates of (2*S*,5*S*)-6a and (2*S*,5*S*)-6b with benzylbenzylideneamine

The addition of organometallic reagents to the C=N bond of imine derivatives has been well documented in the literature.[10] It′s applications, however, has been severely limited by the poor electrophilicity of the azomethine carbon. The electrophilicity of the carbon atom of the C=N bond can be increased by *N*-alkylation,[11] *N*-oxidation,[12] *N*-acylation,[13] *N*-sulfonylation,[14] and by the use of Lewis acids[15] as external promoters. Our strategy, demonstrated in this paper, is the employment of $BF_3{\cdot}OEt_2$ as the Lewis acid. Based on their different steric demands, 1,3-dioxolan-4-ones (2*S*,5*S*)-**6a** and (2*S*,5*S*)-**6b** were selected for this study. The 1,3-dioxolan-4-ones (2*S*,5*S*)-**6a** was transformed into a nonracemic enolate (2*S*)-**6a** by annihilation of the original stereogenic center at C-5 with a base such lithium bis(trimethylsilyl)amide (LiHMDS) at low temperature. Subsequent reaction of the enolate with benzylbenzylideneamine **9** activated by

$BF_3{\cdot}OEt_2$ (2 equiv.) proceeds under the influence of the temporary stereogenic acetal C-2 center to give a 7:4 diastereomeric mixture of 1,3-dioxolan-4-one amine (2*S*,5*R*,1′*S*)-**10a** and (2*S*,5*R*,1′*R*)-**10a** (Scheme 3).[16] The ratio of these two diastereomers was determined by ^{1}H NMR. From a stereochemical point of view, the addition of benzylbenzylidineamine to enolate (2*S*)-**6a** can provide four diastereoisomers, whose relative distribution depends on two different factors: face selectivity, which controls the stereogenic center at the 2-position, while *Re*/*Si* face simple selectivity the newly formed C-1′-carbon stereocenter (Scheme 3). As show in Scheme 3, enolate (2*S*)-**6a** approaches the benzylbenzylidineamine **9** from the less hindered diasterotopic face, thus only diastereoisomers derived from **TSI** (2*S*,5*R*,1′*S*-configuration, major) and **TSII** (2*S*,5*R*,1′*R*-configuration, minor) were formed. The stereochemistry at the C-1′ position strongly depends on reagents steric requirements. When enolate (2*S*)-**6a** was used as a reaction partner, the selectivity was directed by the small hydrogen substituent at C-5 carbon atom of the enolate, favoring an *Si* face of the imine to the dioxolanone ring with the formation of the (2*S*,5*R*,1′*S*)-**10a** as major product. On the other hand, the reaction of enolate (2*S*)-**6b**, bearing a methyl substituent at C-2, with Lewis acid activated benzylbenzylidineamine **9** also gave a 7:4 diastereomeric mixture of the 1,3-dioxolan-4-one amines (2*S*,5*R*,1′*S*)-**10b** and (2*S*,5*R*,1′*R*)-**10b** (Scheme 3).



Scheme 3

The absolute configuration of the *N*-benzyl-1´-aminodioxolanone (2*S*,5*R*,1′*R*)-**10b** was established from single crystal X-ray analysis.[9] The configuration of (2*S*,5*R*,1′*R*)-**10b** was assigned as 5(*R*) and 1′(*R*) on the basis of the known absolute 2(*S*) configuration of the 1´-amino-*N*-benzyl-2-*t*-butyl-2-methyl-1′,5-diphenyl-1,3-dioxolan-4-one **10b** (Figure 5). The absolute

stereochemistry (*R*) at C-5 confirms the addition of the enolate from the π face opposite to isopropyl or *tert*-butyl group respectively.

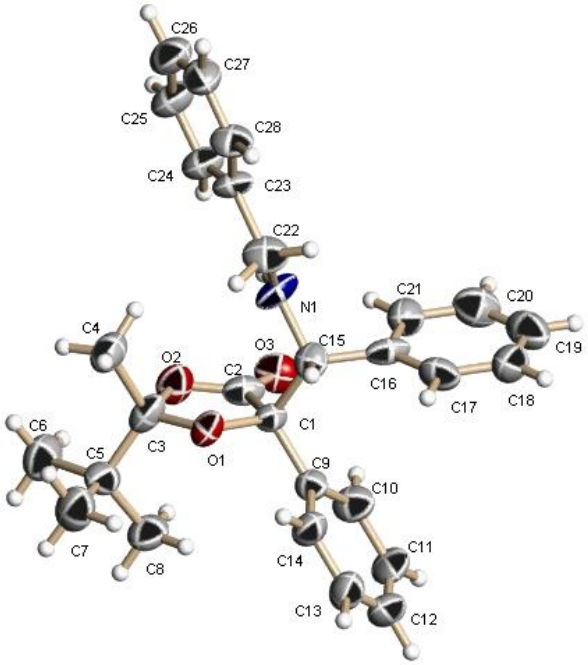
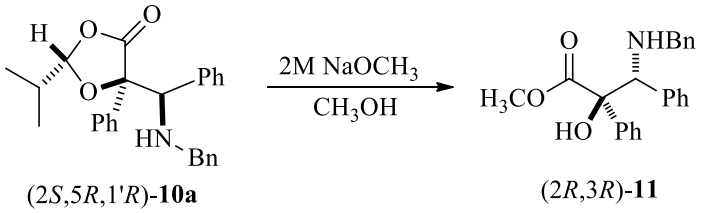


Figure 5. X-ray structure of (2*S*,5*R*,1′*R*)-**10b.**

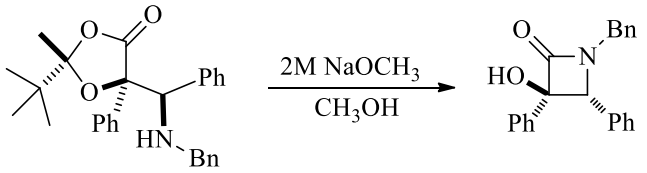
Methanolysis of 1,3-dioxolan-4-one amines (2*S*,5*R*,1′*R*)-10a and (2*S*,5*R*,1′*R*)-10b

In the third part of the present work, we focused our attention on the methanolysis of the derivatives (2*S*,5*R*,1′*R*)-**10a** and (2*S*,5*R*,1′*R*)-**10b**, to the corresponding tetrasubstituted isoserine derivatives (2*R*,3*R*)-**11** and (3*R*,4*R*)-**12**. Thus, treatment of **10a** with NaOMe/MeOH at room temperature for 3.5 h provided α-hydroxy-α,β-diphenyl-β-amino ester (2*R*,3*R*)-**11** in 81 % yield (see Scheme 4). Under the same conditions, (2*S*,5*R*,1′*R*)-**10b** was unaffected, but at reflux temperature the β-lactam, 4-phenyl-3-hydroxy-β-lactam (3*R*,4*R*)-**12** was formed instead. (Scheme 5).



(2*S*,5*R*,1'*R*)-**10a** (2*R*,3*R*)-**11**

Scheme 4



(2*S*,5*R*,1'*R*)-**10b** (2*R*,3*R*)-**12**

Scheme 5

Conclusions

We have developed an efficient two-step protocol for synthesis of trisubstituted α-hydroxy-α,β-diphenyl-β-amino ester (2*R*,3*R*)-**11** starting from (*S*)-mandelic acid **4**. This reagent is converted into active 1,3-dioxolan-4-one (2*R*,5*S*)-**6a**, (2*S*,5*S*)-**6a**, (2*R*,5*S*)-**6b** and (2*S*,5*S*)-**6b** by acetalization with isobutyraldehyde **5a** or pinacolone **5b**. In the second step, the corresponding (2*S*)-enolates are reacted with Bn(BF_3)N=CHPh imine to afford 6-aminodioxolanones (2*S*,5*R*,1′*S*)-**10a**, (2*S*,5*R*,1′*R*)-**10a**, (2*S*,5*R*,1′*S*)-**10b** and (2*S*,5*R*,1′*R*)-**10b**. The acetal group of the dioxolanone ring is removed under base induced alcoholysis to obtain α-hydroxy-α,β-diphenyl-β-amino ester (2*R*,3*R*)-**11** when the acetal group is isobutyraldehyde derivative but when the acetal group is pinacolone derivatives we obtained 3-phenyl-3-hydroxy-β-lactam (3*R*,4*R*)-**12**. This method should provide a useful tool for synthesis of various α-hydroxy-β-amino esters with quaternary stereocenters.

Experimental Section

General. Flasks, stirring bars, and glass syringes used for the generation and reactions of organolithium reagents were oven-dried for ca. 12 h at 120 ºC and allowed to cool in a desiccator over anhydrous $CaSO_4$. Anhydrous solvents were obtained by distillation from benzophenone ketyl [15]. TLC was performed on Merck-DC-F_{254} plates, detection was made by shining UV light. Flash column chromatography was performed using Merck silica gel (230-240 mesh). All melting points are uncorrected. ^{1}H NMR spectra were recorded on a JEOL Eclipse+400 (400 MHz) spectrometer. ^{13}C NMR spectra were recorded on a JEOL Eclipse+400 (100 MHz) spectrometer. Chemical shifts (δ) are indicated in ppm downfield from internal TMS used as reference; the coupling constants (*J*) are given in Hz. Optical rotations were measured in 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 preparation of 1,3-dioxolan-4-one (2*R*,5*S*)-6a, (2*S*,5*S*)-6a, (2*R*,5*S*)-6b and (2*S*,5*S*)-6b

In a 250 mL round-bottom with a Dean-Stark trap was placed (1.0 equiv) of (*S*)-mandelic acid **4** in 150 mL of CH_2Cl_2, (1.1 equiv) of isobutyraldehyde **5a** or pinacolone **5b** in the presence of catalytic amounts of *p*-toluenesulfonic acid and five drops of conc. H_2SO_4 and the resulting solution was refluxed for 12 h or 24 h with azeotropic removal of the water formed. The resulting solution was washed twice with 80 mL of aq. 10% $NaHCO_3$ and the organic phase was dried (Na_2SO_4), filtered and concentrate at reduced procedure.

2-Isopropyl-5-phenyl-1,3-dioxolan-4-one. (2*R*,5*S*)-6a, (2*S*,5*S*) 6a

The general procedure was followed using 2.0 g (13.14 mmol) of (*S*)-mandelic acid **4**, 1.31 mL (13.14) of isobutyraldehyde **5a** and in the presence of catalytic amounts of *p*-toluenesulfonic acid and five drops of conc. H_2SO_4 to give 2.61 g (97%) of the crud product as 4:5 (*trans*/*cis*) mixture, which was purified by flash column chromatography (hexane-ethyl acetate; 98:2) to afford 0.98 g (38%) of (2*R*,5*S*)-**6a** as a colorless oil, $[\alpha]_D^{20}$ = - 0.48° (*c* = 1.0, $CHCl_3$) and 1.27 g (49%) of (2*S*,5*S*)-**6a** as white crystals, $[\alpha]_D^{20}$ = + 81.7° (*c* = 1.0, $CHCl_3$) [lit.[17] $[\alpha]_D^{20}$ = + 82.3° (*c* = 1.0, $CHCl_3$)], mp 50-52 °C [lit.[17] 52-54 °C].

(2*R*,5*S*)-6a. ^{1}H NMR ($CDCl_3$) δ 7.33-7.47 (m, 5H); 5.55 (dd, *J* = 5.0 Hz, J = 1.1 Hz, 1H); 5.37 (s, 1H); 2.06 (m, 1H); 1.06 (d, *J* = 7.0 Hz, 3H); 1.04 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR ($CDCl_3$;) δ 171.5; 134.1; 128.9; 126.0; 108.8; 75.5; 32.9; 15.8; 15.7. Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.89; H, 6.84. Found: C, 69.46; H, 6.93.

(2*S*,5*S*)-6a. ^{1}H NMR ($CDCl_3$) δ 7.38-7.47 (m, 5H); 5.45 (dd, *J* = 8.0 Hz, *J* = 1.1 Hz, 1H); 5.23 (d, *J* = 1.0 Hz, 1H); 2.13 (m, 1H); 1.10 (d, *J* = 6.9 Hz, 3H); 1.09 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR ($CDCl_3$;) δ 171.9; 133.8; 129.2; 128.8; 127.0; 107.6; 76.8; 32.1; 16.0; 15.9. Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.89; H, 6.84. Found: C, 69.46; H, 6.93.

2-*t*-Butyl-2-methyl-5-phenyl-1,3-dioxolan-4-one. (2*R*,5*S*)-6b, (2*S*,5*S*) 6b

The general procedure was followed using 2.0 g (13.14 mmol) of (*S*)-mandelic acid **4**, 1.66 mL (13.14 mmol) of pinacolone **5b** and in the presence of catalytic amounts of *p*-toluenesulfonic acid and five drops of conc. H_2SO_4 to give 2.91 g (94%) of the crud product as (6:5). (*trans*/*cis*) mixture, which was purified by flash column chromatography (hexane-ethyl acetate; 98:2) to afford 1.14 g (37%) of (2*R*,5*S*)-**6b** as a white crystals, mp 86-88°C, $[\alpha]_D^{20}$ = + 67.3° (*c* = 1.0, $CHCl_3$), mp 74-75°C and 1.08 g (35%) of (2*S*,5*S*)-**6a** as a white crystals, $[\alpha]_D^{20}$ = + 76.08° (*c* = 0.5, $CHCl_3$).

(2*R*,5*S*)-6b. ^{1}H NMR ($CDCl_3$) δ 7.33-7.50 (m, 5H); 5.41 (s, 1H); 1.63 (s, 3H); 1.09 (s, 9H). NMR ^{13}C NMR ($CDCl_3$;) δ 171.8; 135.6; 128.8; 125.9; 117.0; 77.4; 40.4; 24.7; 27.7. Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.48; H, 7.94.

(2*S*,5*S*)-6b. ^{1}H NMR ($CDCl_3$) δ 7.34-7.51 (m, 5H); 5.38 (s, 1H); 1.61 (s, 3H); 1.10 (s, 9H). ^{13}C NMR ($CDCl_3$;) δ 171.8; 133.8; 129.0; 128.7; 127.0; 115.6; 75.6; 38.5; 24.8; 19.4. Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.81; H, 7.94.

5-Benzyl-2-isopropyl-1,3-dioxolan-4-one. (2*R*,5*S*)-8a, (2*S*,5*S*) 8a

The general procedure was followed using 2.0 g (12.04 mmol) of (*S*)-phenyllactic acid **7**, 1.20 mL (13.25 mmol) of isobutyraldehyde **5a** and in the presence of catalytic amounts of *p*-toluenesulfonic acid and five drops of conc. H_2SO_4 to give 2.56 g (96%) of the crud product as (2:1). (*trans*/*cis*) mixture, which was purified by flash column chromatography (hexane-ethyl acetate; 98:2) to afford 1.19 g (47%) of (2*R*,5*S*)-**8a** as a colorless oil, $[\alpha]_D^{20}$ = + 43.2° (*c* = 1.0, $CHCl_3$) and 0.98 g (38%) of (2S,5S)-**8a** as a colorless oil, $[\alpha]_D^{20}$ = - 77.8° (*c* = 1.0, $CHCl_3$).

(2*R*,5*S*)-8a. ^{1}H NMR ($CDCl_3$) δ 7.25-7.33 (m, 5H); 5.01 (dd, *J* = 4.8 Hz, *J* = 1.1 Hz, 1H); 4.62 (ddd, *J* = 6.0 Hz, *J* = 4.4 Hz, *J* = 1.1 Hz, 1H); 3.14 (dd, *J* = 14.3 Hz, *J* = 4.4 Hz, *J* = 4.4 Hz, 1H); 3.06 (dd, *J* = 14.3 Hz, *J* = 6.0 Hz, 1H); 1.88 (m, 1H); 0.92 (d, *J* = 7.0 Hz, 1H); 0.91 (d, *J* = 7.0 Hz, 1H). ^{13}C NMR ($CDCl_3$;) δ 172.9; 135.6; 129.7; 128.7; 127.3; 108.9; 75.4; 37.2; 33.0; 15.7; 15.5. Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32. Found: C, 70.88; H, 7.31.g

(2*S*,5*S*)-8a. ^{1}H NMR ($CDCl_3$) δ 7.22-7.33 (m, 5H); 5.24 (dd, *J* = 4.6 Hz, *J* = 1.1 Hz, 1H); 4.49 (ddd, *J* = 7.3 Hz, *J* = 4.0 Hz, *J* = 1.1 Hz, 1H); 3.23 (dd, *J* = 14.7 Hz, *J* = 3.9 Hz, 1H); 3.05 (dd, *J* = 14.7 Hz, *J* = 7.3 Hz, 1H); 1.82 (m, 1H); 0.91 (d, *J* = 6.8 Hz, 3H); 0.89 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR ($CDCl_3$;) δ 174.1; 137.0; 131.0; 129.8; 127.0; 108.4; 76.9; 36.5; 32.1; 16.7; 16.6. Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32. Found: C, 70.75; H, 7.28.

5-Benzyl-2-*t*-butyl-2-methyl-1,3-dioxolan-4-one. (2*R*,5*S*)-8b, (2*S*,5*S*) 8b

The general procedure was followed using 2.0 g (12.04 mmol) of (*S*)-phenyllactic acid **7**, 1.65 mL (13.25 mmol) of pinacolone **5b** and in the presence of catalytic amounts of *p*-toluenesulfonic acid and five drops of conc. H_2SO_4 to give 2.73 g (91%) of the crud product as (2:3). (*trans*/*cis*) mixture, which was purified by flash column chromatography (hexane-ethyl acetate; 98:2) to afford 0.99 g (37%) of (2*R*,5*S*)-**8b** as a white crystals, $[\alpha]_D^{20}$ = + 51.7° (*c* = 0.5, $CHCl_3$), mp 79-80 °C and 1.2 g (44%) of (2*S*,5*S*)-**8b** as a colorless oil, $[\alpha]_D^{20}$ = + 75.4° (*c* = 0.3, $CHCl_3$).

(2*R*,5*S*) 8b. ^{1}H NMR ($CDCl_3$) δ 7.23-7.32 (m, 5H); 4.66 (dd, *J* = 8.3 Hz, *J* = 3.7 Hz, 1H); 3.14 (dd, *J* = 14.4 Hz, *J* = 4.8 Hz, 1H); 3.08 (dd, *J* = 14.4 Hz, *J* = 7.3 Hz, 1H); 1.04 (s, 3H); 0.94 (s, 9H). ^{13}C NMR ($CDCl_3$) δ 173.0, 135.9, 130.2, 128.4, 127.1, 116.8, 77.1, 40.3, 38.7, 24.5, 22.0. Anal. Calcd for $C_{15}H_{20}O_3$: C, 72.55, H, 8.12. Found: C, 72.74, H, 8.16.

(2*S*,5*S*) 8b. ^{1}H NMR ($CDCl_3$) δ 7.23-7.33 (m, 5H, H); 4.58 (dd, *J* = 8.3 Hz, *J* = 3.7 Hz); 3.20 (dd, *J* = 14.3 Hz, *J* = 3.7 Hz, 1H); 3.08 (dd, *J* = 14.3 Hz, *J* = 8.3 Hz, 1H); 1.45 (s, 3H); 0.95 (s, 9H). ^{13}C NMR ($CDCl_3$;) δ 172.8; 136.6; 129.6; 128.6; 127.0; 112.7; 74.8; 38.0, 37.3; 24.5; 19.5. Anal. Calcd for $C_{15}H_{20}O_3$: C, 72.55, H, 8.12. Found: C, 72.59, H, 8.05.

General procedure of the synthesis of *N*-benzyl-1´-aminodioxolanones: (2*S*,5*R*,1′*S*)-10a-b and (2*S*,5*R*,1′*R*)-10a-b

In a 50 mL round-bottom flask fitted with a magnetic bar was placed 1.0 equiv. of (2*S*,5*S*)-**6a** or (2*S*,5*S*)-**6b** in 25 mL of dry THF under nitrogen. The flask was cooled at -78 ºC and 1.0 equiv. of 1.0 M LiHMDS was added *via* syringe. The resulting solution was allowed to react for 20 min. then the benzylbenzylidineamine **9** activated by 2 equiv. of $BF_3{\cdot}OEt_2$ as electrophile was slowly added (prepared in other round-bottom flask). The reaction mixture was then stirred at -78 ºC for 20 h. The reaction mixture was quenched with 15 mL of saturated aq. NH_4Cl, and the product was extracted with CH_2Cl_2 (3 x 50 mL). The combined extracts were dried over anhydrous $MgSO_4$, and concentrate at reduced procedure.

1'-amino-*N*-benzyl-2-isopropyl-1',5-diphenyl-1,3-dioxolan-4-one. (2*S*,5*R*,1′*S*)-10a and (2*S*,5*R*,1′*R*) (10a). The general procedure was followed using 0.39 g (1.88 mmol) of (2*S*,5*S*)-**6a** in 25 mL of THF, 2.10 mL of LiHMDS, 0.37 g (1.88 mmol) of benzylbenzylidineamine **9** and 0.37 mL of $BF_3{\cdot}OEt_2$, to give 0.80g (93%) of the crud product and ^{1}H NMR analysis showed a mixture of two diastereomeric products in a 7:4 ratio, which was purified by TLC chromatography (hexane-ethyl acetate; 90:10) to afford 40 mg of (5%) of (2*S*,5*R*,1′*S*)-**10a** as a colorless oil, $[\alpha]_D^{20}$ = -13.1º (*c* = 0.17, $CHCl_3$) and 70 mg (10%) of (2*S*,5*R*,1′*R*)-**10a** as a white crystals, $[\alpha]_D^{20}$ = + 7.13º (*c* = 0.04, $CHCl_3$), mp 112-112 ºC.

(2*S*,5*R*,1′*S*)-10a. ^{1}H NMR ($CDCl_3$) δ 7.43-7.00 (m, 15H); 5.60 (d, *J* = 5.9 Hz, 1H); 4.18 (s, 1H); 3.70 (d, J_A = 13.2 Hz, 1H); 3.61 (d, J_B = 12.8 Hz, 1H); 1.95 (br, 1H, NH); 1.84 (*m*, 1H); 1.02 (d, *J* = 6.7 Hz, 3H); 0.94 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR ($CDCl_3$;) δ 173.4; 139.8; 137.6; 137.2; 128.7; 128.6; 128.5; 128.4; 128.3; 128.0; 127.8; 127.1; 125.3; 109.5; 86.1; 69.7; 51.6; 33.9; 16.5; 16.4. HRMS (FAB+) calc. for $C_{26}H_{28}NO_3$ (MH^+) 402.2069; found 402.2066

(2*S*,5*R*,1′*R*)-10a. ^{1}H NMR ($CDCl_3$) δ 7.72-6.82 (m, 15H); 4.60 (d, *J* = 5.8 Hz, 1H); 4.17 (s, 1H); 3.64 (d, J_A = 13.9 Hz, 1H); 3.26 (d, J_B = 13.9 Hz, 1H); 1.75 (m, 1H); 0.94 (d, *J* = 6.9 Hz, 3H); 0.82 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR ($CDCl_3$;) δ 172.1; 139.3; 136.9; 136.7; 130.2; 129.54; 128.6; 128.4; 128.3; 128.1 127.0; 125.4; 120.0; 109.0; 85.6; 67.6; 50.6; 33.5; 16.3; 16.2. HRMS (FAB+) calc. for $C_{26}H_{28}NO_3$ (MH^+) 402.2069; found 402.2066

1'-amino-*N*-benzyl-2-*t*-butyl-2-methyl-1′,5-diphenyl-1,3-dioxolan-4-one. (2*S*,5*R*,1′*S*)-10b and (2*S*,5*R*,1′*R*) (10b). The general procedure was followed using 0.30 g (1.28 mmol) of (2*S*,5*S*)-**6b** in 25 mL of THF, 1.62 mL of LiHMDS, 0.25 g (1.28 mmol) of benzylbenzylidineamine **9** and 0.37 mL of $BF_3{\cdot}OEt_2$, to give 0.43 g (79%) of the crud product and ^{1}H NMR analysis showed a mixture of two diastereomeric products in a 7:4 ratio, which was purified by TLC chromatography (hexane-ethyl acetate; 90:10) to afford 60 mg (11%) of (2*S*,5*R*,1′*S*)-**10b** as a white crystals, $[\alpha]_D^{20}$ = + 21.78º (*c* = 0.74, $CHCl_3$) mp 130-132 ºC and 50 mg (10%) of (2*S*,5*R*,1′*R*)-**10b** as white crystals, $[\alpha]_D^{20}$ = + 10.78º (*c* = 0.90, $CHCl_3$), mp 125-127 ºC.

(2*S*,5*R*,1′*S*)-10b. ^{1}H NMR ($CDCl_3$) δ 6.97-7.28 (m, 15H); 3.96 (s, 1H); 3.67 (d, J_A = 13.2 Hz, 1H); 3.59 (d, J_B = 13.2 Hz, 1H); 1.67 (s, 3H); 0.81 (s, 9H). ^{13}C NMR ($CDCl_3$;) δ 172.9; 139.9;

138.1; 138.0; 128.8; 128.3; 128.2; 127.9; 127.6; 127.53; 127.5; 127.0; 125.8; 116.2; 87.2; 70.5; 52.1; 39.6; 25.3; 22.4. HRMS (FAB+) calc. for $C_{28}H_{32}NO_3$ (MH^+) 430.2382; found 430.2368.

(2*S*,5*R*,1′*R*)-10b. ^{1}H NMR ($CDCl_3$) δ 7.52-6.94 (m, 15H); 4.10 (s, 1H); 3.64 (d, J_A = 13.5 Hz, 1H); 3.32 (d, J_B = 13.5 Hz, 1H); 1.24 (s, 3H); 0.78 (s, 9H, H-10). ^{13}C NMR ($CDCl_3$;) δ 172.3; 139.7; 136.9; 136.8; 128.6; 128.3; 128.0; 127.9; 127.9; 127.7; 126.9; 126.3; 116.4; 85.7; 69.5; 51.2; 39.6; 25.2; 22.4. HRMS (FAB+) calc. for $C_{28}H_{32}NO_3$ (MH^+) 430.2382; found 430.2368.

Synthesis of α-hydroxy-β-amino ester. (2*R*,3*R*) (11). In a 50 mL round-bottom flask with a magnetic bar was placed 10 mg (0.03 mmol) of (2*S*,5*R*,1′*R*)-**10a** with 2 mL of MeOH, The resulting solution was cooled in an ice-water bath before addition of 0.03 mL (0.03 mmol) of 1.0 M MeONa. The reaction mixture was then stirred at 25 ºC for 5 h and was concentrated in a rotary evaporator. The residue was dissolved in 100 mL of CH_2Cl_2, washed three times with H_2O. The organic phase was dried over anh. Na_2SO_4 and concentrated in the rotary evaporator to afford 7.6 mg (81%) of (2*R*,3*R*)-**11** as a colorless oil, $[\alpha]_D^{20}$ = + 14.82º (*c* = 0.108, $CHCl_3$).

(2*R*,3*R*)-10. ^{1}H NMR ($CDCl_3$) δ 7.71-6.98 (m, 15H); 4.42 (s, 1H); 3.67 (d, J_A = 13.5 Hz, 1H); 3.32 (d, J_B = 13.5 Hz, 1H); 3.50 (s, 3H). ^{13}C NMR ($CDCl_3$;) δ 173.6; 139.8; 139.7; 138.2; 129.3; 128.4; 128.2; 128.1, 128.0; 126.9; 126.6; 81.3; 66.7; 52.8; 50.7. Anal. Calcd for $C_{23}H_{23}NO_3$: C, 76.43, H, 6.41. Found: C, 76.13, H, 6.63.

Synthesis of β-Lactam. (3*R*,4*R*) (12). In a 50 mL round-bottom flask with a magnetic bar was placed 10 mg (0.02 mmol) of (2*S*,5*R*,1′*R*)-**10b** with 2 mL of MeOH. The resulting solution was cooled in an ice-water bath before addition of 0.02 mL (0.02 mmol) of 1.0 M MeONa. The reaction mixture was then stirred at 25 ºC for 5 h and then 3 h at reflux and was concentrated in a rotary evaporator. The residue was dissolved in 100 mL of CH_2Cl_2, washed three times with H_2O. The organic phase was dried over anh. $MgSO_4$ and concentrated in the rotary evaporator to afford 7.2 mg (94%) of (3*R*,3*R*)-**12** as a yellow crystals, $[\alpha]_D^{20}$ = - 12.1º (*c* = 0.148, $CHCl_3$). mp 83.4-84.7 ºC

(3*R*,3*R*)-12. ^{1}H NMR ($CDCl_3$) δ 7.32-6.83 (m, 15H); 4.98 (d, J_A = 15.0 Hz, 1H); 3.87 (d, J_B = 15.0 Hz, 1H); 4.72 (s, 1H), 4.05 (br, 1H, OH). ^{13}C NMR ($CDCl_3$;) δ 170.2; 136.1; 134.9; 134.2; 128.9; 128.7; 128.4; 128.2; 128.1; 127.9; 127.5; 91.4; 69.6; 44.4. Anal. Calcd for $C_{22}H_{19}NO_2$: C, 80.22, H, 5.81. Found: C, 79.55, H, 5.75.

Acknowledgements

We are indebted to Conacyt, Mexico for financial support via grants 91338 and 84453. We are indebted to Prof. Joseph M. Muchowski for many friendly discussions.

References and Notes

1. (a) Manich, C.; Krösche, W. Arch. Pharm. **1912**, *250*, 647. (b) Arend, M.; Westermann, B.; Risch, N. *Angew. Chem. Int. Ed. Engl*. **1998**, *37*, 1044. (c) Cordova, A. *Acc. Chem. Res.* **2004**, *37*, 102. (d) Weiner, B.; Szymański, W.; Dick B. Janssen, D. B.; Minnaarda, A. J.; Feringa, B.L. *Chem. Soc. Rev*. **2010**, *39*, 1656.
2. (a) Guénard, D.; Guéritte-Voegelein, F.; Lavelle, F. *Current Pharmaceutical Design* **1995**, *1*, 95. (b) Ichinose, Y.; Genka, K.; Koike, T.; Kato, H.; Watanabe, Y.; Mori, T.; Lioka, S. Sakuma, A.; Ohta, M. *J. Natl. Cancer Inst.* **2003**, *95*, 605.
3. Montiel-Smith, S.; Cervantes-Mejía, V.; Dubois, J.; Guénard, D.; Guéritte, F.; Sandoval-Ramírez, J. *Eur. J. Org. Chem.* **2002**, 2260.
4. Huang, H.; Guo, X.; Hu, W. *Angew. Chem. Int. Ed.* **2007**, *46*, 1337.
5. (a) Liu, X.; Deng, L.; Jiang, X.; Yan, W.; Liu. C.; Wang, W. *Org. Lett.* **2010**, *12*, 876. (b) Deiana, L.; Zhao, G. –L.; Dzedzic, P.; Rios, R.; Vesely, J.; Ekström, J.; Córdova, A. *Tetrahedron Lett.* **2010**, *51*, 234. (c) Periasamy, M.; Ganesan, S. S.; Suresh, S. *Tetrahedron: Asymmetry* **2010**, *21*, 385. (d) Giampietro, N. C.; Wolfe, J. P. *Angew. Chem. Int. Ed.* **2010**, *49*, 2922.
6. (a) Battaglia, A.; Barbaro, G.; Giorgianni, P.; Guerrini, A.; Bertucci, C.; Geremia, S. *Chem. Eur. J.* **2000**, *6*, 3551. (b) Guerrini, A.; Varchi, G.; Samoì, C.; Daniele, R.; Battaglia, A. *Tetrahedron Lett*. **2007**, *48*, 5081. (c) Barbaro, G.; Battaglia, A.; Cuerrini, A.; Bertucci, Geremia, S. *Tetrahedron: Asymmetry* **1998**, *9*, 3401. (d) Barbaro, G.; Battaglia, A.; Guerrini, A. *J. Org. Chem*. **1999**, *64*, 4643. (e) Guerrini, A.; Varchi, G.; Battaglia, A. *J. Org. Chem*. **2006**, *71*, 6785.
7. (a) Chapel, N.; Greiner, A.; Ortholand, J.–Y. *Tetrahedron Lett*. **1991**, *32*, 1441. (b) N.; Greiner, A.; Ortholand, J.–Y. *Tetrahedron Lett*. **1990**, *31*, 2135. (c) Seebach, D.; Naef, R.; Calderari, G. *Tetrahedron* **1984**, *40*, 1313.
8. Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem*. **1978**, *43*, 2923.
9. Crystallographic data (excluding structure factors) for the compounds in this papers have been deposited with the Cambridge Crystallographic Data Centre as supplementary material publications number CCDC803862 [(2*S*,5*S*)-**6b**], CCDC803863 [(2*R*,5*S*)-**6b**], CCDC803865 [(2*R*,5*S*)-**8b**], CCDC803864 [(2*S*,5*R*,1′*R*)-**10b**]
10. (a) Bloch, R. *Chem. Rev*. **1998**, *98*, 1407. (b) Friestad G. K.; Mathies A. K. *Tetrahedron* **2007**, *63*, 2541. (c) Enders, D.; Reinhold, U.; *Tetrahedron: Asymmetry* **1997**, *8*, 1895.
11. Leonard, N. J.; Paukstelis, J. V. *J. Org. Chem.* **1963**, *28*, 3021.
12. Bonnett, R.; Clark, V. M.; Todd, A. *J. Chem. Soc.* **1959**, 2102.
13. Böhme, H.; Ebel, S.; Hartke, K. *Chem. Ber.* **1965**, *98*, 1463.
14. Ueda, M.; Miyaura, N. *J. Organomet. Chem.* **2000**, *595*, 31.
15. (a) López-Ruiz, H.; Mera-Moreno, I.; Rojas-Lima, S.; Santillán, R.; Farfán, N. *Tetrahedron Lett.* **2008**, *49*, 1674. (b) Agarwal, S.; Knölker, H. -J. *Org. Biomol. Chem.* **2004**, *2*, 3060. (c)

Brown, H. C.; Kramer, G. W.; Levy, A. B.; Midland, M. M. *Organic Synthesis via Boranes*; Wiley, New York, 1975; p. 256.

16. Without $BF_3{\cdot}OEt_2$ no reaction addition was observed and only we recovered the starting material or the corresponding diastereoisomer as an epimer in C-5. Attempts to improve the yields and selectivity using $Al[(CH_3)_2CHO]_3$, $AlCl_3$, $Ti[OCH(CH_3)_2]_4$ and *n*-Bu_2BOTf were unsuccessful and no Mannich addition adducts were obtained.
17. (a) Mashraqui, S. H.; Kellogg, R. M. *J. Org. Chem.* **1984**, *49*, 2513. (b) Krysan, D. J.; Mackenzie, P. B. *J. Am. Chem. Soc.* **1988**, *100*, 6273.

