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Synthesis of Optically Active Constrained 2-Substituted Norstatines: A Straightforward Application of Seebach's "SRS" Synthetic Principle

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A straightforward two-step methodology of synthesis of optically active (2*R*)-substituted norstatines via addition of *N-tert*-butoxycarbonyl-substituted aldimines to (2*S*)-chiral enolates of 1,3-dioxolan-4-ones has been developed. In particular, the use of the natural (2*S*)-malic acid is examined for the synthesis of potential GABAergic spirocyclic γ-lactams.

Introduction

Specific peptide-based inhibitors of peptidases, which incorporate β-amino acid residues into substrates, have shown an extraordinary biological stability compared to the normally incorporated α-amino acids and exhibit remarkable biological activity.[1] In recent years, the discovery of α,α-disubstituted β-amino acids in natural bioactive compounds have been attracting biochemical interest in connection with the design and synthesis of constrained analogues.[2] Moreover, when incorporated into peptides their conformational restraints induce a large variety of stable secondary structures.[3] In fact, an important aspect of this family is their ability to fold into well defined and stable helices, turns, pleated sheets, etc. Among the β-amino acid family, statine and norstatine,[4] and their structurally modified analogues, are probably the most important members because they are found in a variety of natural products and pharmaceutical substances, such as Taxol, and have been widely used in the design of peptidomimetics as inhibitors of proteases.[5] For instance, a set of isosters containing the statines and norstatine scaffolds, including bestatine, JE-2147, and KNI-272, are potent HIV-1-PR inhibitors.[6]

Statine- and norstatine-based compounds[7] are also very active against malaria proteases expressed by the parasite *Plasmodium falcifarum*, plasmepsins I−II,[8] which are responsible of the hemoglobin degradation pathway, as well as the human protease cathepsin D. This protease is overexpressed in several cases of breast cancer[9] and is associated with an increased risk for Alzheimer's disease.[10]

Minor attention has been paid to the synthesis, conformational, and biological activity studies of chiral α-substituted norstatines. It is worth noting that the

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synthesis of constrained analogues of active compounds is a common procedure adopted in medicinal chemistry to restrict the possible low energy conformations.[11] Provided that the activity is still retained, this less flexible analogue can reach the binding site more easily. Synthetic procedures of the *syn*-(2*R*) members of norstatines were especially developed to target constrained analogues bearing aliphatic substituents at the C-2 position of the isoserine chain of taxanes and endowed of higher cytotoxic activity of the parent paclitaxel and docetaxel,[12] as well as racemic *syn*-norstatines bearing an aromatic substituent at C-2.[13] Instead, only one methodology is reported regarding the synthesis of asymmetric *anti*-α-substituted norstatines with moderate selectivity.[14] This protocol finds a serious limit due to a poor availability of the starting reagents, i.e., the (*R*)-3-amino-3-phenylpropanoic acid and the (*S*)-3-aminobutanoic acid, which were obtained in racemic form and resolved by enzymatic hydrolysis. These reagents gave *anti*-(2*S*,3*S*)-epimers of 3-phenyl and 3-methyl derivatives of 3-benzoylamino-2-alkylnorstatines (alkyl = Me, Et, *n*-Pr, allyl, benzyl), respectively. Another limit of this protocol was the type of substituent at the nitrogen, which was restricted only to the benzoylamino group.

While β-amino acid oligomers form well-defined stable secondary structures in solution, such as helices,[15] pleated sheets,[16] and turns,[17] geminally dialkyl-substituted derivatives do not fit into any of these major structures.[18] Thus, the stereochemical effects of the simultaneous presence of an alkyl and a hydroxyl group on the quaternary C-2 stereogenic center on secondary structures is not easily predictable.[19] As a consequence, additional methodologies are required to selectively target all four epimers of the trisubstituted 2-alkyl-

CHART 1

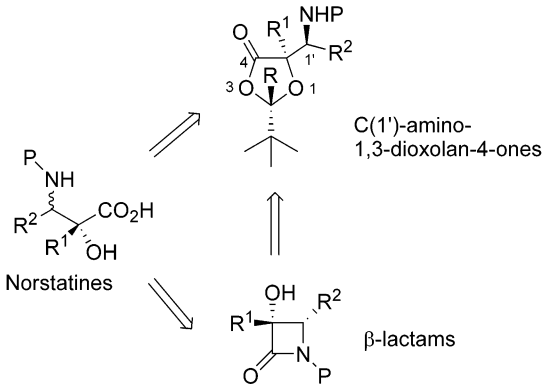


CHART 2

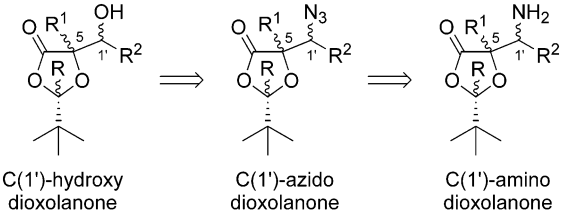
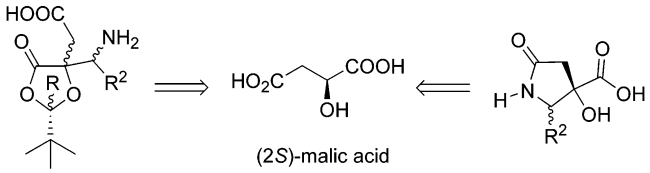


CHART 3



norstatines. Our interest in the development of novel procedures for the synthesis of 2-substituted norstatines was stimulated by our previous studies on the chemistry of (3*R*)-3-hydroxy-3-substituted β-lactams[20] and (2*S*,5*R*,1′*S*)-1′-amino-1,3-dioxolanones,[21] which were shown to be chemically interconnected using suitable methodologies (Chart 1).

To date, C(1′)-amino dioxolanones are only prepared by conversion of the C(1′)-hydroxy group of dioxolanone alcohols to the corresponding C(1′)-azido followed by reduction (Chart 2). A major problem with this protocol is that the synthesis of dioxolanone alcohols lacked stereochemical control at both C−(5) and C−(1′).[22]

In this paper, we will explore a variant of our β-lactam protocol, which directly targets 1′-aminodioxolanones as equivalents of conformationally restricted and fully protected 2-substituted norstatines. In particular, we will examine the use of (2*S*)-malic acid as a natural precursor of either a particular type of 1′-aminodioxolanones bearing an additional workable carboxyethyl appendant or cyclic conformationally restrained norstatines (Chart 3).

Results and Discussion

Our protocol follows Seebach's "self-regeneration of stereocenters" synthetic principle (SRS),[23] and it has been

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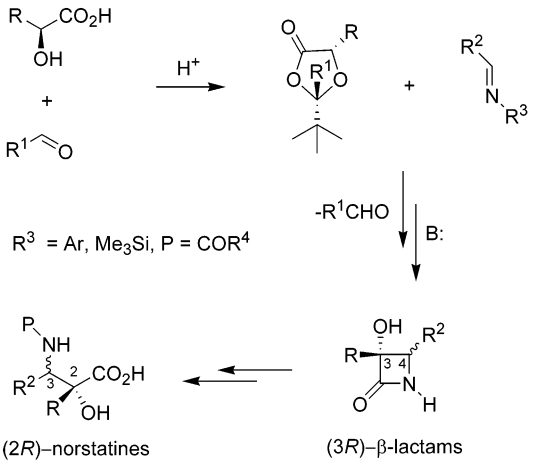
SCHEME 1



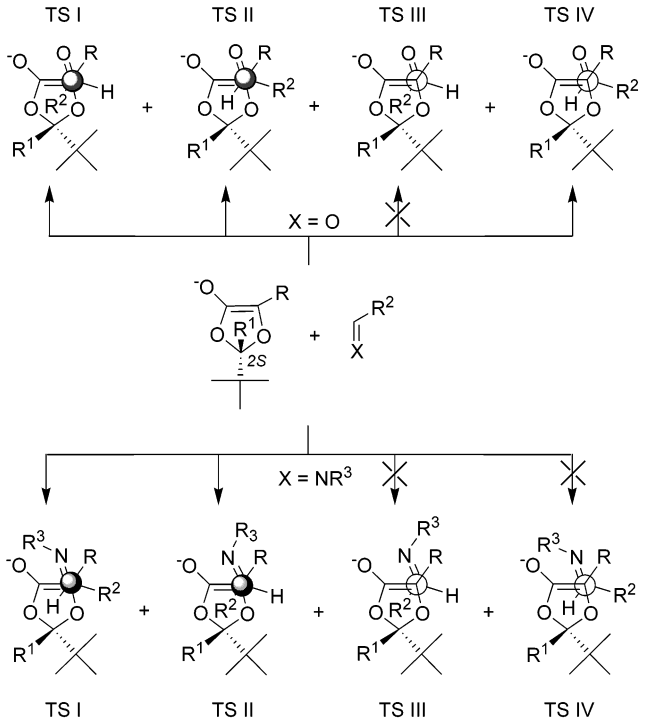
applied to addition reactions of (2*S*)-chiral enolates of 1,3-dioxolan-4-ones to a number of imines in a versatile and predictable manner (Scheme 1). Major vantage of this method is that dioxolanon-4-ones are readily available from the acetalization of inexpensive natural (*S*)-α-hydroxycarboxylic acids, and aldeydes or ketones such as pivalaldehyde or pinacolone. Usually, these lactones are obtained as major (2*S*,5*S*)-isomers of (2*S*,5*S*)/(2*R*,5*S*) diasteromeric mixtures but can be isolated as pure homochiral material via fractional crystallization at low temperatures.

When *N*-trimethlylsilylimines were the partners, the addition to the enolate, the cyclization, and the removal of the auxiliary center directly afforded the corresponding (3*R*)-3-hydroxy-3-alkyl-*β*-lactams in good yields, full (3*R*)-stereocontrol, and moderate to good selectivity at position 4.

The full (3*R*)-stereocontrol of these reactions was rather gratifying since the "SRS" synthetic principle fails to provides good diastereoselectivity in aldol condensations of enolates of dioxolanones with aldehydes or ketones due to a lack of face stereochemical control at the (2*S*)-stereocenter of the enolate.[22,24] The different behavior of imines and aldehydes is not unexpected when comparing the stereochemical outcome of the reaction of an aldehyde, or an imine, to (2*S*)-enolate of a dioxolanone (Scheme 2). Four possible stereoisomers can be in principle obtained from a reaction of an aldehyde or an imine with the (2*S*)-enolate of a dioxolanone. Two stereoisomers are formed via transition states TS I and TS II. The other two stereoisomers are formed via the transition states TS III and TS IV. Transition states TS I and TS II are kinetically favored over TS III and TS IV because the aldehyde, or the imine, approaches the enolate from the less hindered enantiotopic face which bear the small R^1 substituent. No products of addition are formed via transition state TS III due to the severe interaction between the R^2 substituents of the aldheyde, or the imine, with the *tert*-butyl substituent.

By contrast, the hydrogen atom of the aldehyde in transition state TS IV does not interact significantly with

SCHEME 2. Stereochemical Outcome of the Addition Reactions of the (2*S*)-Enolate of a Dioxolanone with an Aldehyde (X = O) or an Aldimine (X = NR^3)



the *tert*-butyl substituent, this allowing the formation of consistent amounts of the corresponding products of condensation. When an imine is the partner of the enolate in TS IV, the presence of the hydrogen and the bulky R^3 substituent at the carbon and nitrogen atoms, both oriented toward the *tert*-butyl substituent, inhibit the formation of products of the corresponding stereoisomers. As a consequence, random mixtures of three stereoisomers, derived from TS I, TS II, and TS IV, are obtained with aldehydes. Instead, imines only afford *β*-lactams derived from transition states TS I and TS II whose common feature is the presence of the (3*R*)-stereogenic center which bears the HO and the R substituents. Remarkably, this methodology affords the corresponding enantiomeric (3*S*)-*β*-lactams, provided that (2*R*)-α-hydroxy carboxylic acids, easily available from the corresponding naturally occurring (2*S*)-α-amino acids, are the starting reagents. Sequential protection of the 3-hydroxy group of the (3*R*)-*Z*- and (3*S*)-*Z*-*β*-lactams, acylation of the nitrogen atom and base induced ring opening[25] affords the corresponding (2*R*)-*syn*- or (2*S*)-*syn*-α-hydroxy-*β*-amino acids (norstatines), respectively.

In this paper, a variant of this protocol, which uses *N*-*tert*-butoxycarbonyl (*N*-BOC)-protected aldimines[26] bearing a phenyl (**4**) or a 2-thienyl substituent (**5**), will be examined. These partners were selected for their high electrophilicity, which favors the attack to the sterically demanding enolates of dioxolanones **1**−**3**. At the same

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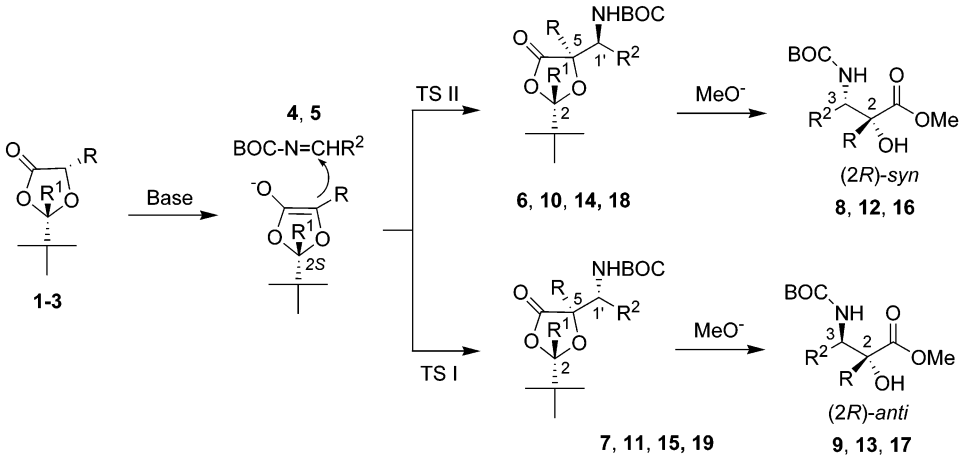
SCHEME 3



1: R = R^1 = Me; **2**: R = C_6H_5, R^1 = H; **3**: R = CH_2COOH, R^1 = H; **4**: R^2 = C_6H_5; **5**: R^2 = 2-Thienyl;
6-9: R = R^1 = Me, R^2 = C_6H_5; **10-13**: R = R^1 = Me, R^2 = 2-Thienyl;
14-17: R = C_6H_5; R^1 = H, R^2 = 2-Thienyl; **18-19**: R = CH_2COOH, R^1 = H, R^2 = 2-Thienyl

TABLE 1. Yields and Product Distribution of 1′-Aminodioxolanones 6, 7, 10, 11, 14, 15, 18, and 19

entry	reagents	products (yield (%), % ee[a])	product yield (%, % ee[a])	diastereomeric ratio (overall yields (%))
1	**1** + **4**	(2*S*,5*R*,1′*S*)-**6** (25, 86)	(2*S*,5*R*,1′*R*)-**7** (63, 86)	**6/7** = 0.4/1.0 (88)
2	**1** + **5**	(2*S*,5*R*,1′*R*)-**10** (15, 86)	(2*S*,5*R*,1′*S*)-**11** (68, 86)	**10/11** = 0.2/1.0 (83)
3	**2** + **5**	(2*S*,5*R*,1′*R*)-**14** (63, 100)	(2*S*,5*R*,1′*S*)-**15** (18, 100)	**14/15** = 3.6/1.0 (81)
4	**3** + **5**	(2*S*,5*R*,1′*R*)-**18** (31, 96)	(2*S*,5*R*,1′*S*)-**19** (31, 96)	**18/19** = 1.0/1.0 (62)[b]

[a] Determined by enantioselective HPLC analysis. [b] 82% conversion.

time, the electron-withdrawing acyl substituent is expected to prevent the cyclization step to β-lactam. Even so, the sterical requirements of the transition states derived from *N*-BOC-imines are similar to those derived from imines leading to the formation of β-lactams. This allowed the isolation of C(1′)-*N*-BOC-amino-1,3-dioxolan-4-ones **6**, **7**, **10**, **11**, **14**, **15**, **18**, and **19** only derived from TS I and TS II (Scheme 3) in which the absolute stereochemistry at C(5) is conserved.[27]

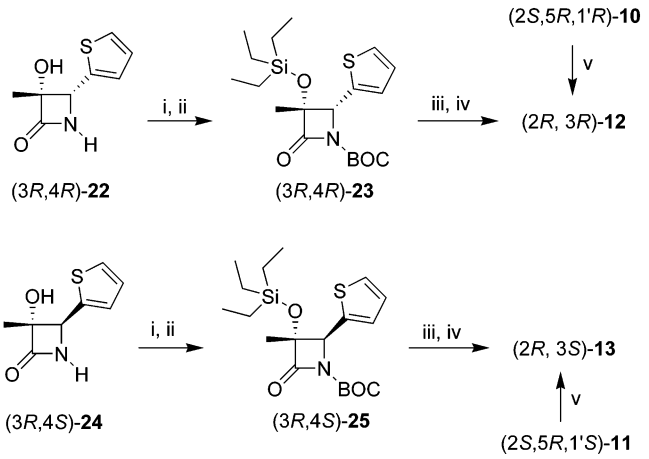
These heterocycles can be considered as suitable protected norstatines bearing two orthogonal protecting groups: the BOC substituent at the nitrogen atom which can be removed under mild acidic conditions and the acetal protecting group of the carboxy and the adjacent alcoholic substituents which can be opened under basic conditions. Finally, the heteroaromatic aldimine **5** was selected to explore the possibility of insertion of the thiophene group into the framework of the constrained norstatine, since it well mimics the phenyl group of phenyl alanine, an amino acid commonly found in HIV-protease inhibitors.[28] Partners of the imines **4** and **5** were the dioxolan-4-ones **1**−**3**. The lactone **1** was obtained, and directly used, as a (2*S*,5*S*)/(2*R*,5*S*) = 93:7 mixture by acetalization of (*S*)-lactic with pinacolone.[29] The acetalization of (*S*)-mandelic and (*S*)-malic acids with pivalaldeide, respectively, gave the lactone **2**, as pure homochiral material, and compound **3** which was isolated, and directly used, as a (2*S*,5*S*)/(2*R*,5*S*) = 98:2 mixture.[30] The treatment of dioxolanones **1**−**3** with lithium (bis)trimethylsilyl amide gave their nonracemic (2*S*)-lithium enolates which were reacted with imines **4** and **5** in the mixed solvent THF/HMPA = 85:15 at low temperatures (−80/−50 °C).

Yields, product distribution, and enantiomeric excesses (% ee) of the 1′-aminodioxolanones **6**, **10**, **14**, and **18** and their diastereomers **7**, **11**, **15**, and **19** are reported in Table 1.

The mixtures of pair of epimers[31] (2*S*,5*R*,1′*S*)-**6**/(2*S*,5*R*,1′*R*)-**7** and (2*S*,5*R*,1′*R*)-**10**/(2*S*,5*R*,1′*S*)-**11** were separated by chromatography, while compounds (2*S*,5*R*,1′*R*)-**14**/(2*S*,5*R*,1′*S*)-**15** and (2*S*,5*R*,1′*R*)-**18**/(2*S*,5*R*,1′*S*)-**19** were isolated as mixtures. MeO^--induced methanolysis of the acetal auxiliary of the pair **6/7**, **10/11**, and **14/15** yielded the methyl isoserinates (2*R*,3*S*)-**8**/(2*R*,3*R*)-**9**, (2*R*,3*R*)-**12**/(2*R*,3*S*)-**13**, and (2*R*,3*R*)-**16**/(2*R*,3*S*)-**17**. This allowed the stereochemical assessment of the 1′ -aminodioxolanones **6**−**7** and **10**−**11** by chemical correlation methods. In fact, (2*S*,5*R*,1′*S*)-**6** was chemical correlated with the ester (2*R*,3*S*)-*syn*-**8**, synthesized via an independent route.[21] Similarly, (2*R*,3*R*)-*syn*-**12** was chemically correlated to the (3*R*,4*R*)-*Z*-β-lactam **22**[20] (Scheme 4) according to the following procedure. The hydroxy group and the nitrogen atoms of **22** were sequentially

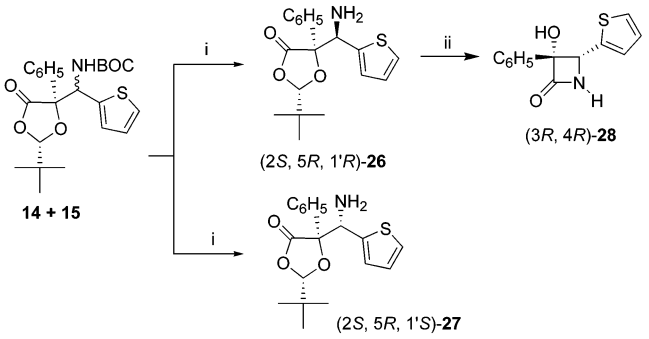
(27) It is worth noting that the use of *N*-acylated imines as the partenters of dioxolanones, prevents the formation of unwanted byproducts derived from an addition to the enolate of pivalaldehyde formed during the cyclizzation step to the β-lactam.
(28) Gante, J. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1699−1720.
(29) Ortholand, Y. J.; Greiner, A. *Bull. Soc. Chim. Fr*. **1993**, *130*, 133−142.
(30) Seebach, D.; Naef, R.; Calderari, G. *Tetrahedron* **1984**, *40*, 1313−1324.
(31) Even if compounds **6**, **10**, **14**, and **18** possess an identical stereochemistry, the inversion in the descriptor of the 1′ position of compound **6** (1′*S*) with respect to **10**, **14**, and **18** (1′*R*) is due to the priority rule at this stereocenter.

SCHEME 4[a]



[a] Reagents: (i) TesCl/imidazole; (ii) BOC_2O/DMAP; (iii) MeOH, Et_3N, DMAP; (iv) TBAF in THF; (v) MeO^-/MeOH.

SCHEME 5[a]



[a] Reagents: (i) TFA/HCO_3^-; (ii) LHMDS/THF/HMPA, 15:1/−50 °C.

silylated and carbonylated, according to usual protocols,[12b] to give the (3*R*, 4*R*)-*Z*-β-lactam **23**. Methanolysis of **23**,[32] followed by desilylation, gave the target (2*R*,3*R*)-*syn*-**12**, thus allowing the stereochemical assessment of the 1′-aminodioxolanone (2*S*,5*R*,1′*R*)-**10**. An identical chemical correlation between the (3*R*,4*S*)-*E*-β-lactam **24** and (2*R*,3*S*)-*anti*-**13**, via the fully protected β-lactam **25**, was also performed. Finally, *N*-BOC deprotection of (2*S*,5*R*, 1′*R*)-**14** and (2*S*,5*R*,1′*S*)-**15** with trifluoro acetic acid yielded the 1′-aminodioxolanones (2*S*,5*R*,1′*R*)-**26** and (2*S*,5*R*,1′*S*)-**27** (Scheme 5). The two epimers were separated by chromatography. The major isomer (2*S*,5*R*,1′*R*)-**26** was converted into the corresponding β-lactam (3*R*, 4*R*)-**28** by LHMDS-induced cyclization. The stereochemistry of **28** was assessed by NOE and HSQC difference spectra. In fact, the relevant connection of the HSQC was that of the two ortho−ortho′ carbon atoms of the aromatic ring at 125.6 ppm and the directly linked ortho−ortho′ protons which absorbed in the region between 7.54 and 7.58 ppm. The irradiation of these two aromatic protons showed a consistent NOE of 3% with CHN proton at 5.06 ppm and vice versa, while the irradiation of OH group at 3.3 ppm showed an NOE of 2.5% with one of the hydrogen atoms of the thiophene ring at 7.10 ppm. Full stereocontrol in the reactions involving the (2*S*)/(2*R*) = 93:7 mixture of the enolate of **1** and the homochiral (2*S*)-enolate of **2** was confirmed by enantioselective HPLC analysis the final diastereomeric pairs of isoserines **8** and **9**, **12** and **13**, and **16** and **17**. In fact, compounds **8**, **9**, **12**, and **13** were obtained as enantiomeric couples in a 93:7 ratio (86% ee) while **16** and **17** were obtained as pure homochiral material. This result indicated that the addition of the imines **4** and **5** to the enolates of **1** and **2** occurred under total facial-diastereocontrol since the obtained ee correspond to that expected on the basis of the diastereomeric excesses (de) of **1** and **2**.

As opposed to other 1′-aminodioxolanones, the 1:1 product distribution of the (2*S*)-malic acid derivatives (2*S*,5*R*,1′*R*)-**18** and (2*S*,5*R*,1′*S*)-**19** was confirmed by HPLC analysis. These compounds served for the synthesis of β-amino acids **29** and **30** whose conformational restriction is due to the presence of the quaternary stereogenic center in a rigid cyclic spirolactone structure.

In fact, the treatment of **18** and **19** with TFA in anhydrous conditions favored a sequential deprotection of the *N*-BOC group with the formation of γ-aminobutyric acid derivatives and their spontaneous cyclization to the corresponding γ-lactams (2-pyrrolidones) (2*S*,5*R*,1′*S*)-**29** and (2*S*,5*R*,1′*R*)-**30**, respectively (Scheme 6).[33] Conformationally constrained 2-pyrrolidinones, bearing a quaternary stereogenic center, are found in biologically active molecules, such as inhibitors of proteases[34] and cholesterol absorption,[35] antibiotics,[36] and GABAergic agonists.[37] In our case, these heterocycles are substituted in various positions with precise configurations and are conformationally constrained in a spirocyclic γ-lactam structure as in the agonist GBP-L.[38]

The structures of **29** and **30** were assessed by ASIS effect of the aromatic 2-thienyl substituent and qualitative homonuclear NOE experiments. In fact, the acetal H-2 proton of (2*S*,5*R*,1′*S*)-**29** absorbed at 4.0 ppm, upfield to that of (2*S*,5*R*,1′*R*)-**30** (5.3 ppm), since it is strongly shielded by the 2-thienyl substituent (Figure 1). In line with these findings, the irradiation of the *tert*-butyl substituent of (2*S*,5*R*,1′*S*)-**29** at 0.81 ppm caused an enhancement of one of the two protons, Ha of the CH_2 group of the oxazolidone ring which located on the same face centered at 2.66 ppm (Scheme 6). Consequently, the irradiation of the geminal Hb proton caused an enhancement of 1′-H at 5.35 ppm (4%).

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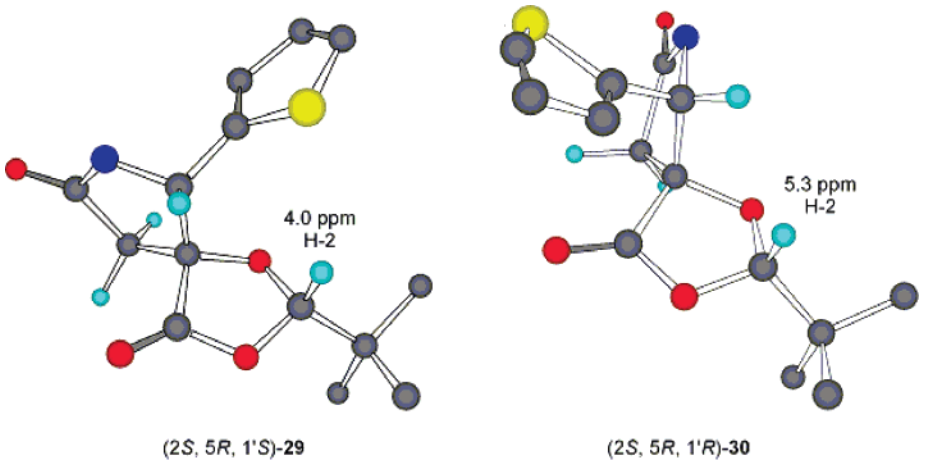
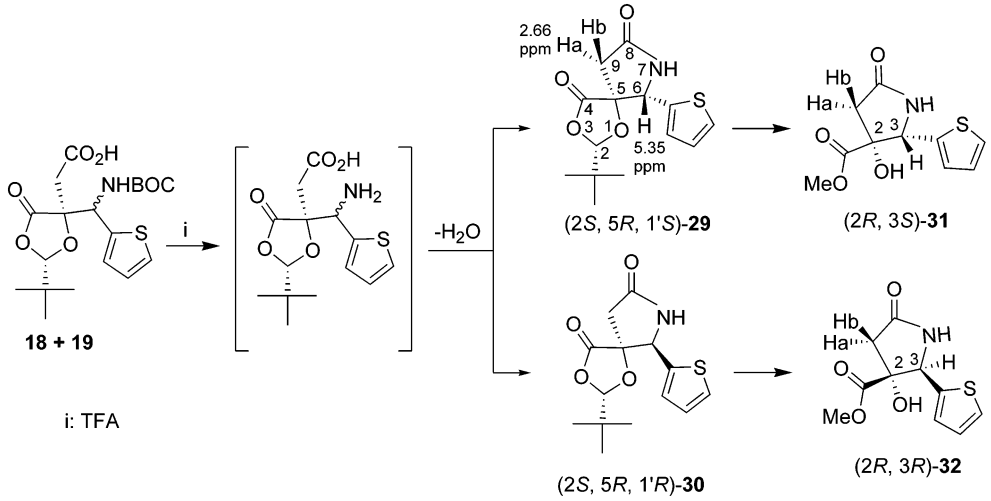


FIGURE 1. ChemBats3D picture of **29** and **30**.

SCHEME 6



Removal of the acetal auxiliary of **29** and **30** by MeO^--induced methanolysis yielded the corresponding methyl isoserinates (2*R*,3*S*)-**31** and (2*R*,3*R*)-**32**, respectively. NOE experiments allowed the assessment of their stereochemistry, which were fully consistent with those of their parent **29** and **30**. The irradiation of the HO group at 3.96 ppm of (2*R*,3*R*)-**32** showed NOE of 3% with C3-H and 1% with the Ha proton of the CH_2 group of the oxazolidone ring located on the same face. The irradiation of this proton showed an NOE of 2% with the C3-H proton. Consistently, the irradiation of the 2-OH group of the isomer (2*R*,3*S*)-**31** (in CD_3COCD_3) gave an NOE of 2% with the Ha proton of the CH_2 group centered at 2.46 ppm, while the irradiation of the Hb proton at 2.97 ppm gave an NOE of 2% with the C3-H proton at 5.44 ppm. Moreover, ASIS effect of the aromatic 2-thienyl substituent shifted upfield the 2-OH proton (2.92 ppm) of (2*R*,3*S*)-**31**, with respect to that of (2*R*,3*R*)-**32** (3.96 ppm).

Conclusions

We have developed an efficient two-step protocol for synthesis of trisubstituted α-hydroxy-α-substituted-*β*-amino acids starting from naturally and economically available (2*S*)-hydroxy acids. In the first step, these reagents are converted into optically active (2*S*,5*S*)-dioxolan-4-ones by acetalization with pivalaldehyde or pinacolone. In the second step, the corresponding (2*S*)-enolates are reacted with *N*-BOC imines to afford α-hydroxy-α-substituted *β*-amino acids orthogonally protected at the nitrogen atom and the acetal α-OH group in a form of *N*-BOC-1′-aminodioxolanones. In fact, the BOC protecting group is removed under acidic conditions, such as TFA or formic acid, while the acetal group of the dioxolanone ring is removed under base-induced alcoholysis. A proper choice of substituents in the reagents allowed a preliminary investigation on the diastereoselectivity of these reactions. Products are obtained with total (2*R*)-stereocontrol at the 2-position of the amino acid (5 of the 1′-aminodioxolanone) due to a preferential approach of the sterically demanding imine to the less hindered face of the dioxolanone ring. The variable 3*R* or 3*S* selectivity (1′*R* or 1′*S* of the 1′-aminodioxolanone) depends on the steric demand of the substituent at C-5 of dioxolanone and the substituent at the carbon atom of the imine (Scheme 2). When a small methyl substituent is present at C-5, a *syn* relationship between the two substituents is preferred in the transition state. As a consequence, the 1′-aminodioxolanone epimers which afforded the *anti*-isoserines as the major products were

obtained (entries 1 and 2 of Table 1). A similar selectivity was also found in the formation of β-lactams when the diphenyl imine was the partner of the enolate of **1**.[20] An *anti* approach is favored with the dioxolanones **2** and **3** which bear more sterically hindered C-5 substituents (C_6H_5 and CH_2COOH, entries 3 and 4).

A quite interesting application of this methodology is the synthesis of α-hydroxy-β-amino acids from malic acid whose conformational constrain is due to the presence of a γ-lactam cyclic structure typical of GABAergic products which opens new perspectives in the synthesis of pharmacologically active peptidomimetics. Evaluation of biological activity data for spirolactones **29** and **30** and their derivatives **31** and **32** is currently underway.

Experimental Section

General Procedure for Synthesis of 1-Aminodioxolanones. A THF solution of dioxolanone (2.0 mL × 0.25 g of dioxolanone) was added dropwise at −78 °C to a THF solution (10.0 mL × 0.25 g of dioxolanone) of LHMDS (1.4 equiv, 1.0 M in THF). The solution was left at this temperature for 25 min, and then HMPA (2.5 mL in 2.0 mL of THF × 0.25 g of dioxolanone) was added. The temperature was lowered at −90 °C, and after 5 min a THF solution (2.0 mL) of freshly prepared *N*-BOC-imine (1.5 equiv) was added dropwise. The temperature was kept at −80 °C for 1 h, then raised to −50 °C over 2 h, and left at this temperature for 1 h. The reaction was quenched at this temperature with HCl 1.0 N and warmed, under stirring, at room temperature. The reaction solution was washed three times with 0.2 N HCl and then with saturated NH_4Cl to completely remove the cosolvent HMPA and extracted with ethyl acetate. The organic phase was dried and evaporated in vacuo. The diasteromers were purified or separated, when possible, by chromatography.

Synthesis of (2*S*,5*R*,1′*S*)- and (2*S*,5*R*,1′*R*)-2-*tert*-Butyl-5-(1′-*tert*-butoxycarbonylamino-1′-phenylmethyl)-2,5-dimethyl-1,3-dioxolan-4-ones [(2*S*,5*R*,1′*S*)-6 and (2*S*,5*R*,1′*R*)-7]. A 0.30 g (1.74 mmol) sample of **1** (93:7 mixture) and imine **4** gave a 1:2.5 mixture of **6/7**. Chromatography (SiO_2, *n*-hexane/Et_2O/CH_2Cl_2, 16:1:2) gave 0.017 g (0.44 mmol, 25%) of (2*S*,5*R*,1′*S*)-**6** and 0.415 g (1.10 mmol, 63%) of (2*S*,5*R*,1′*R*)-**7**. (2*S*,5*R*,1′*S*)-**6**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.25−7.35 (m, 5 H), 5.70−5.84 (d, 1 H), 4.80−4.94 (d, 1 H), 1.54−1.58 (b, 3 H), 1.38 (s, 9 H, 3 Me), 0.95 (s, 9 H, 3 Me), 0.64−0.68 (b, 3 H, Me); ^{13}C NMR ($CDCl_3$) δ 175.0, 155.0, 139.0, 129.0, 128.5, 116.8, 82.6, 80.2, 60.5, 39.3, 28.5, 25.5, 24.0, 21.7; $[\alpha]^{20}_D$ + 21.0 (*c* 0.7, $CHCl_3$); IR (Nujol, cm^{-1}) 3420,1790, 1715, 1708, 1490, 1367, 1151; MS *m/z* 378, 347, 321, 291, 229, 206, 173, 150. Anal. Calcd for $C_{21}H_{31}NO_5$: C, 66.82; H, 8.28; N, 3.71. Found: C, 67.03; H, 8.17; N, 3.65. (2*S*,5*R*,1′*R*)-**7**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.20−7.45 (m, 5 H), 5.40 (d, 1 H, *J* = 9.0 Hz), 5.16 (d, 1 H), 1.47 (s, 3 H), 1.30−1.43 (b, 9 H, 3 Me), 1.00 (s, 3 H), 0.90−1.00 (b, 9 H, 3 Me); ^{13}C NMR ($CDCl_3$) δ 173.5, 155.0, 137.6, 128.3, 128.0, 127.9, 115.6, 82.6, 80.0, 59.9, 38.9, 28.3, 25.3, 25.0, 22.3; $[\alpha]^{20}_D$ + 26.0 (*c* 0.5, $CHCl_3$); IR (Nujol, cm^{-1}) 3423,1794, 1719, 1702, 1493, 1367, 1151; MS *m/z* 378, 347, 321, 291, 229, 206, 173, 150. Anal. Calcd for $C_{21}H_{31}NO_5$: C, 66.82; H, 8.28; N, 3.71. Found: C, 66.68; H, 8.35; N, 3.74.

General Procedure for the Synthesis of β-Aminoesters. To a solution of 1′-aminodioxolanones (3.0 mL × 0.100 g) in dry ethanol were added 1.5 equiv of a freshly prepared solution of 1. 5 M of MeO^- in MeOH. The solution was stirred under nitrogen at 65 °C and monitored by TLC until disappearance of the starting material. After cooling, the reaction was quenched with 0.1 M HCl and extracted with ethyl acetate. The solution was dried and evaporated under vacuo. The residue was chromatographed (SiO_2, EtOAc/*n*-hexane, 1:2) to give the aminoesters.

(2*R*,3*R*)-3-(*tert*-Butoxycarbonylamino)-2-hydroxy-2-methyl-3-phenylpropionic Acid Methyl Ester (2*R*,3*R*)-9. (2*S*,5*R*,1′*R*)-**7** (0.30 g, 0.79 mmol) gave (2*R*,3*R*)-**9** (0.177 g, 0.75 mmol, 95%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.20−7.35 (m, 5 H), 5.64 (d, 1 H, *J* = 9.0 Hz), 4.94 (d, 1 H), 3.62 (s, 3 H, OMe), 3.15−3.25 (b, 1 H), 1.57 (s, 3 H, Me), 1.42 (s, 9 H, 3 Me); ^{13}C NMR ($CDCl_3$) δ 175.5, 155.8, 138.5, 128.5, 128.2, 127.7, 79.9, 77.7, 59.8, 53.0, 28.6, 23.6; $[\alpha]^{20}_D$ −30.0 (*c* 1.0, $CHCl_3$); IR (Nujol, cm^{-1}) 2109, 1739; MS *m/z* 235 (M^+), 208, 193, 158, 148, 133, 106. Anal. Calcd for $C_{16}H_{23}NO_5$: C, 62.12; H, 7.49; N, 4.53. Found: C, 61.95; H, 7.60; N, 4.48

Synthesis of β-Lactams (3*R*,4*R*)-23 and (3*R*,4*S*)-25. These β-lactams were prepared from (3*R*,4*R*)-**22** and (3*R*,4*S*)-**24**, respectively, according to a two-step protocol described in ref 12b. Compound **23** was prepared in 84% overall yields with respect to the starting **22** while **25** was prepared in 80% with respect to **24**. (3*R*,4*R*)-**23**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.25−7.30 (m, 1H), 6.90−7.0 (m, 2H), 4.99 (s, 1 H), 1.64 (s, 3 H), 1.43 (s, 9 H, 3 Me), 0.82 (t, 9 H, 3 Me), 0.50−0.60 (m, 6 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.0, 148.3, 138.0, 127.1, 126.6, 125.9, 85.5, 83.8, 65.3, 28.1, 27.6, 6.6, 6.0; $[\alpha]^{20}_D$ + 54.3 (*c* 0.9, $CHCl_3$); IR (Nujol, cm^{-1}) 2960, 1815, 1722; MS *m/z* 397, 342, 297, 268, 225. Anal. Calcd for $C_{19}H_{31}NO_4SSi$: C, 57.39; H, 7.86; N, 3.52. Found: C, 57.58; H, 7.80; N, 3.44. (3*R*,4*S*)-**25**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.28−7.30 (m, 1H, 7.0−7.5 (m, 1H, 6.94−6.98 (m, 1H, 5.03 (s, 1 H), 1.44 (s, 9 H, 3 Me), 1.21 (s, 3 H, Me), 0.98 (t, 9 H, 3 Me), 0.68−0.78 (m, 6 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.0, 148.0, 138.3, 127.1, 125.5, 125.0, 87.7, 83.7, 66.3, 27.9, 19.1, 6.7, 5.9; $[\alpha]^{20}_D$ − 63.1 (*c* 0.5, $CHCl_3$); IR (Nujol, cm^{-1}) 2955, 1811, 1717; MS *m/z* 397, 342, 297, 268, 225. Anal. Calcd for $C_{19}H_{31}NO_4SSi$: C. 57.39; H, 7.86; N, 3.52. Found: C. 57.18; H, 7.94; N, 3.60.

Synthesis of (2*S*,5*R*,1′*R*)- and (2*S*,5*R*,1′*S*)-2-*tert*-Butyl-5-(1′-amino-1′-(2-thienyl)methyl-5-phenyl-1,3-dioxolan-4-ones [(2*S*,5*R*,1′*R*)-26 and (2*S*,5*R*,1′*S*)-27]. To a mixture of dioxolanones **14/15** = 3.6:1 (0.120 g, 0.278 mmol) was added a solution of 0.36 mL of TFA in CH_2Cl_2 (6.0 mL) for 30 min at 0 °C and 5.0 h at 20 °C. The solvent was evaporated, and the residue was dissolved in 5.0 mL of MeOH/H_2O 1:1, and then 3.0 mL of a 0.5 M aqueous solution of $NaHCO_3$ was added. The mixture was extracted with EtOAc, dried, and evaporated under vacuo. The residue was chromatographed (SiO_2, EtOAc/*n*-hexane, 1:3) to afford (2*S*,5*R*,1′*R*)-**26** (0.066 g, 0.198 mmol, 71%) and (2*S*,5*R*,1′*S*)-**27** (0.018 g, 0.055 mmol, 20%). (2*S*,5*R*,1′*R*)-**26**: $[\alpha]^{20}_D$ −42.0 (*c* 1.1, $CHCl_3$); IR (Nujol, cm^{-1}) 3387, 3323, 2961,1789, 1602, 1483, 1198; MS *m/z* 331, 316, 173, 156, 112; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.58 (d, 2 H, arom), 7.22−7.30 (m, 3 H, arom), 7.15 (d, 1 H, arom), 6.78 (m, 1 H), 6.60 (m, 1 H), 5.62 (s, 1 H), 4.73 (s, 1 H), 1.90 (b, 2H), 0.95 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 173.5, 142.8, 136.8, 128.2, 128.1, 126.3, 125.9, 125.5, 125.3, 111.8, 86.2, 61.3, 35.6, 23.8. Anal. Calcd for $C_{18}H_{21}NO_3S$: C, 65.23; H, 6.39; N, 4.23. Found: C, 65.01; H, 6.45; N, 4.16. (2*S*,5*R*,1′*S*)-**27**: $[\alpha]^{20}_D$ +81.9 (*c* 0.6, $CHCl_3$); IR (Nujol, cm^{-1}) 3385, 3321, 2964,1789, 1607, 1485, 1200; MS *m/z* 331, 316, 173, 156,112; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.82 (d, 2 H), 7.35−7.45 (m, 3 H), 7.33 (d, 1 H) 7.15 (m, 1 H), 7.00 (m, 1 H), 4.83 (s, 1 H), 4.55 (s, 1 H), 1.58 (b, 2H, NH_2), 0.84 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 172.5, 142.5, 136.3, 128.7, 127.2, 126.3, 125.9, 125.6, 110.9, 86.1, 59.7, 35.5, 23.7. Anal. Calcd for $C_{18}H_{21}NO_3S$: C. 65.23; H, 6.39; N, 4.23. Found: C. 65.28; H, 6.48; N, 4.14.

Synthesis of 3-Hydroxy-3-phenyl-4-(2-thienyl)azetidin-2-one (3*R*,4*R*)-28. The reaction of (2*S*,5*R*,1′*R*)-**26** (0.066 g, 0.198 mmol) with 2.5 equiv of LHMDS in a mixed solvent THF/HMPA (95:5) at −50 °C gave after 1 h the β-lactam (3*R*, 4*R*)-**28** (0.042 g, 0.172 mmol, 87%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.54−7.58 (m, 2 H),7.38−7.46 (m, 4 H), 7.09−7.0 (m, 2 H), 6.77 (s, 1 H), 5.06 (s, 1 H), 3.35 (b, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.4, 139.3, 137.9, 129.1, 129.0, 128.0, 126.9, 126.8, 125.6, 89.4, 63.4; $[\alpha]^{20}_D$ −71 (*c* 0.3, $CHCl_3$); IR (Nujol, cm^{-1}) 3275, 1756; MS *m/z* 228 (M^+ − 17), 202, 112. Anal. Calcd for $C_{13}H_{11}NO_2S$: C, 63.65; H, 4.52; N, 5.71. Found: C, 63.45; H, 4.43; N, 5.80.

2-*tert*-Butyl-6-thiophen-2-yl-1,3-dioxa-7-azaspiro[4.4]-nonane-4,8-diones (2*S*,5*R*,1′*S*)-29 and (2*S*,5*R*,1′*R*)-30. To the 1:1 mixture of acids (2*S*,5*R*,1′*S*)-**18**/(2*S*,5*R*,1′*R*)-**19** (0160 g, 0.387 mmol) in anhydrous CH_2Cl_2 (4.0 mL) at 0 °C was added 0.5 mL of TFA. The reaction mixture was left at this temperature for 2 h and 15 h at 25 °C. The solution was concentrated at 20 °C, quenched with 10% $NaHCO_3$, extracted twice with EtOAc, and dried, and the solvent was evaporated. Chromatography (SiO_2, cyclohexane/acetone 17:3) gave (2*S*,5*R*,1′*S*)-**29** (0.047 g, 0.159 mmol, 41%) and (2*S*,5*R*,1′*R*)-**30** (0.049 g, 0.166 mmol, 43%). (2*S*,5*R*,1′*S*)-**29**: $[\alpha]^{20}_D$ + 91.0 (*c* 0.5, $CHCl_3$); IR (Nujol, cm^{-1}) 1792, 1714, 1674, 1231; MS *m/z* 295, 153, 110; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.43 (d, 1 H), 7.13 (d, 1 H), 7.02 (d, 1 H), 6.70 (s, 1 H), 5.35 (s, 1 H), 4.05 (s, 1 H), 3.1 (d, 1 H), 2.65 (d, 1 H), 0.81 (s, 9 H, 3 Me); ^{13}C NMR ($CDCl_3$) δ 173.2, 171.9, 136.2, 128.2, 127.9, 127.2, 110.5, 84.0, 60.8, 41.7, 34.6, 23.2. Anal. Calcd for $C_{14}H_{17}NO_4S$: C, 56.93; H, 5.80; N, 4.74. Found: C, 56.75; H, 5.88; N, 4.70. (2*S*,5*R*,1′*R*)-**30**: $[\alpha]^{20}_D$ −39.0 (*c* 0.4, $CHCl_3$); IR (Nujol, cm^{-1}) 1794, 1713, 1675, 1230; MS *m/z* 295, 153, 110; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.32 (d, 1 H), 7.08 (d, 1 H), 7.03 (d, 1 H) 6.90 (s, 1 H), 5.30 (s, 1 H), 5.23 (s, 1 H), 3.05 (d, 1 H, J = 17.6 Hz), 2.70 (d, 1 H, J = 17.6 Hz), 0.94 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 172.8, 170.0, 138.3, 128.1, 126.6, 126.4, 109.1, 85.1, 62.0, 39.3, 35.0, 23.2. Anal. Calcd for $C_{14}H_{17}NO_4S$: C, 56.93; H, 5.80; N, 4.74. Found: C, 56.80; H, 5.73; N, 4.81.

Supporting Information Available: Experimental details and spectroscopy data for compounds **10**−**19**, **31**, and **32**. This material is available free of charge via the Internet at http://pubs.acs.org.

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