1-methoxy-1,3-cyclohexadiene (0.1 mL, 0.84 mmol) in dichloromethane (20 mL) was stirred at room temperature for 3 days. The solvent was removed on a rotary evaporator, and the resulting colorless solid was washed with ether and dried (0.24 g, 94%): mp 307 °C (CH_2Cl_2–Et_2O); ^1H NMR (200 MHz, $CDCl_3$) δ 8.31–7.07 (m, 12 H), 6.07 (m, 2 H), 4.33 (d, J = 9.5 Hz, 1 H), 3.71 (m, 1 H), 3.54 (d, J = 9.5 Hz, 1 H), 3.47 (s, 3 H), 1.87 (m, 2 H), 1.30 (m, 2 H); IR (KBr) 3474, 3056, 2947, 2869, 1616, 1585, 1379, 1313, 1303, 1287, 1162, 1144, 1125, 1107, 892, 815, 751, 742, 717 cm^{-1}. Anal. Calcd for $C_{29}H_{24}O_5S_2$: C, 67.42; H, 4.68. Found: C, 67.27; H, 4.72.

Reaction of 1 with α-Terpinene. A mixture of 1 (0.1 g, 0.25 mmol), α-terpinene (0.1 mL, 0.61 mmol), and a few crystals of hydroquinone, placed into a screw-capped Pyrex test tube, was purged with nitrogen, sealed, and heated with stirring at 160 °C for 2 h. After cooling the mixture to room temperature, 13 was collected as a colorless solid, which was filtered, washed with cold ether, and recrystallized from dichloromethane–ether (0.90 g, 90%): mp 170–1 °C; ^1H NMR (200 MHz, $CDCl_3$) δ 8.27–6.79 (m, Ar, 12 H), 3.70 (m, 2 H), 3.42 (m, 2 H); IR (KBr) 3057, 2957, 1671, 1584, 1448, 1315, 1128, 1107, 818, 749, 705 cm^{-1}. Anal. Calcd for $C_{22}H_{16}O_4S_2$: C, 64.69; H, 3.95. Found: C, 64.69; H, 3.85.

Reduction of 10h with Sodium Amalgam. Recovery of the Chiral Auxiliary. A mixture of the adduct **10h** (2.0 g, 3.87 mmol) and NaH_2PO_4 (8 g, 66.7 mmol) in dry methanol (25 mL) was purged with nitrogen. Under very efficient stirring, 6% sodium amalgam (8.88 g, ca. 8:1 equivalent ratio sodium to substrate) was added in portions. The reaction mixture was stirred at room temperature and monitored by TLC, eluting with petroleum ether. After 2 h water was added and the reaction mixture was extracted with pentane. The extracts were washed with brine, dried over sodium sulfate, and rotary evaporated to leave essentially pure 14 as a colorless oil (0.39 g, 75%): ^1H NMR (60 MHz, $CDCl_3$) δ 6.42 (d, J = 6.0 Hz, 2 H), 6.27 (t, J = 6.0 Hz, 2 H), 3.67 (br s, 1 H), 3.51 (s, 3 H), 1.32–1.47 (m, 4 H).

The aqueous layer was acidified with dilute HCl and extracted with dichloromethane. The organic layer was dried over magnesium sulfate and rotary evaporated. The residue was refluxed for 1 h in dry THF (50 mL) with a large excess of lithium aluminum hydride (200 mg). Ethyl acetate (50 mL) and HCl (50 mL, 4 N) were added, and the mixture was extracted with dichloromethane. The combined organic solutions were dried (Na_2SO_4) and concentrated to give **2** (0.61 g, 50%) essentially pure by ^1H NMR.

Acknowledgment. Grateful thanks are due to Drs. G. Licini and L. Pasquato for running and interpreting several NMR and NOE spectra for us. The ROESY experiment was carried out by Dr. S. Mammi of the Centro Studi Biopolimeri del CNR (Padova).

Supplementary Material Available: Fractional coordinates with equivalent isotropic thermal parameters and selected bond distances and bond angles for compounds **9**, **10d**, and **12** (9 pages); structure factors for **9**, **10d**, and **12** (44 pages). Ordering information is given on any current masthead page.

α-Oximino Amide Trianions in the Stereoselective Synthesis of Isoxazolines and γ-Hydroxy-α-amino Acids

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The trianions **17** and **33**, which were prepared from the corresponding α-oximino amides **7** and **30**, were reacted with 4-methoxybenzaldehyde to stereoselectively provide, on acidification, the corresponding trans-substituted isoxazoline-3-carboxamides **8** and **31**/**32**, respectively. Additionally, the dianion **24**, which was prepared from the corresponding *O*-silyl oxime **22**, was reacted with 4-methoxybenzaldehyde to stereoselectively give the anti β-hydroxy oxime **23**. Reduction of **8** and **26** stereoselectively gave the 2,3-syn-3,4-anti amino amides **11** and **27**. Amides **11** and **27** were subsequently converted to the γ-hydroxy-α-amino acids **12** and **29** and the corresponding lactones **13** and **28**. Amino acid **29** is the N-terminal amino acid of the antifungal agent nikkomycin B.

Introduction

There are several classes of natural products that contain unusual α-amino acid residues bearing γ-hydroxy groups. Examples include theonellamide F,[1] a marine bicyclic peptide antifungal agent; scytonemin A, a calcium antagonist produced by a blue-green alga;[2] funebrine, a novel pyrrole alkaloid;[3] and the nikkomycins and neopolyoxins,[4,5] which are a group of nucleoside di- and tripeptides noted for their ability to inhibit chitin synthetase. The nikkomycins are exemplified by nikkomycin B (1), nikkomycin X (2), and nikkomycin J (3) (Chart I). These natural products behave as surrogates for uridine diphosphate *N*-acetylglucosamine (4), which is the prepolymer converted by a chitin synthetase into chitin. As a result, the nikkomycins are potentially useful as fungicidal or insecticidal agents.

Both König[5,6] and Jäger[7] have reported synthetic methods for the preparation of the N-terminal amino acid

(1) Matsunaga, S.; Fusetani, N.; Hashimoto, K.; Wälchli, M. *J. Am. Chem. Soc.* **1989**, *111*, 2582.

(2) Helms, G. L.; Moore, R. E.; Niemczura, W. P.; Patterson, G. M. L.; Tomer, K. B.; Gross, M. L. *J. Org. Chem.* **1988**, *53*, 1298.

(3) Raffauf, R. F.; Zennie, T. M.; Onan, K. D.; Le Quesne, P. W. *J. Org. Chem.* **1984**, *49*, 2714.

(4) Uramoto, M.; Kobinata, K.; Isono, K.; Higashijima, T.; Miyazawa, T. *Tetrahedron* **1982**, *38*, 1599. Hagenmaier, H.; Keckeisen, A.; Zähner, H.; König, W. A. *Liebigs Ann. Chem.* **1979**, 1494. Hagenmaier, H.; Keckeisen, A.; Dehler, W.; Fiedler, H.-P.; Zähner, H.; König, W. A. *Ibid.* **1981**, 1018. Rathmann, R.; König, W. A.; Schmalle, H.; Carlsson, G.; Bosch, R.; Hagenmaier, H.; Winter, W. *Ibid.* **1984**, 1216. Delzer, J.; Fiedler, H.-P.; Müller, H.; Zähner, H.; Rathmann, R.; Ernst, K.; König, W. A. *J. Antibiot.* **1984**, *37*, 80. Bormann, C.; Huhn, W.; Zähner, H.; Hahn, H.; König, W. A. *Ibid.* **1985**, *38*, 9. Bormann, C.; Mattern, S.; Schrempf, H.; Fiedler, H.-P.; Zähner, H. *Ibid.* **1989**, *42*, 913. Decker, H.; Bormann, C.; Fiedler, H.-P.; Heitsch, H.; König, W. A. *Ibid.* **1989**, *42*, 230. Heitsch, H.; König, W. A.; Decker, H.; Bormann, C.; Fiedler, H.-P.; Zähner, H. *Ibid.* **1989**, *42*, 711. For a review on the structurally related polyoxins, see: Isono, K.; Suzuki, S. *Heterocycles* **1979**, *13*, 333.

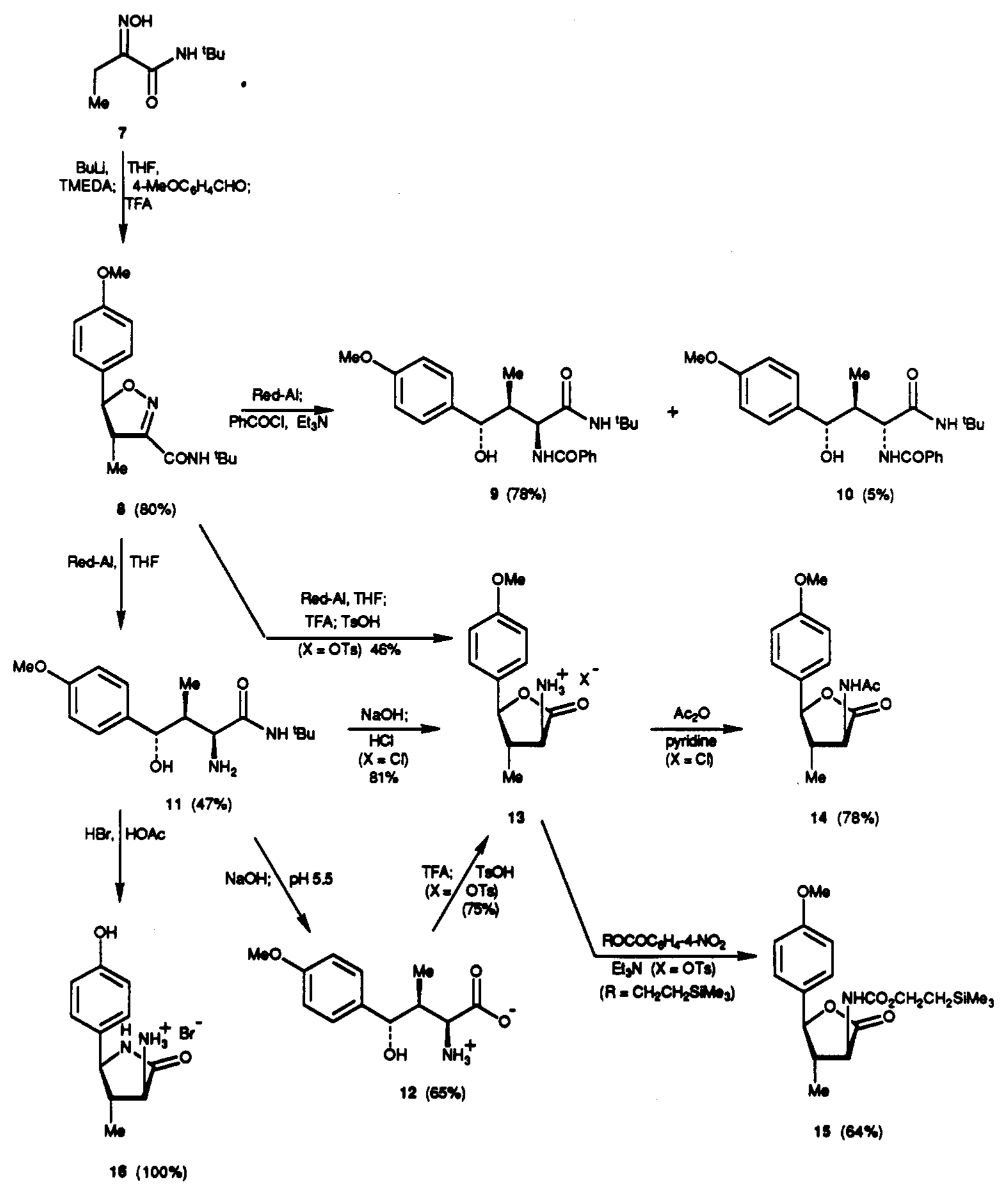
(5) König, W. A.; Hass, W.; Dehler, W.; Fiedler, H.-P.; Zähner, H. *Liebigs Ann. Chem.* **1980**, 622. Hass, W.; König, W. A. *Ibid.* **1982**, 1615. König, W. A.; Hahn, H.; Rathmann, R.; Hass, W.; Keckeisen, A.; Hagenmaier, H.; Bormann, C.; Dehler, W.; Kurth, R.; Zähner, H. *Ibid.* **1986**, 407. Hahn, H.; Heitsch, H.; Rathmann, R.; Zimmerman, G.; Bormann, C.; Zähner, H.; König, W. A. *Ibid.* **1987**, 803.

(6) For the synthesis and absolute stereochemical assignment of the N-terminal amino acid of nikkomycin B (1), see: Zimmermann, G.; Hass, W.; Faasch, H.; Schmalle, H.; König, W. A. *Liebigs Ann. Chem.* **1985**, 2165.

(7) Jäger, V.; Grund, H.; Buss, V.; Schwab, W., Müller, I.; Schone, R.; Franz, R.; Ehrler, R. *Bull. Soc. Chim. Belg.* **1983**, *92*, 1039. Jäger, V.; Müller, I.; Schohe, R.; Frey, M.; Ehrler, R.; Häfele, B.; Schröter, D. *Lect. Heterocycl. Chem.* **1985**, *8*, 79. Franz, R., Ph.D. Thesis, Bayerischen Julius-Maximilians-Universität, Würzburg, 1984.

0022-3263/91/1956-1894$02.50/0

Scheme I



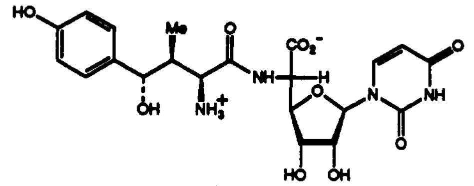
residues of the nikkomycins. These methods use a 1,3-dipolar cycloaddition reaction to construct the racemic[8] isoxazoline carboxylic esters **5**. Subsequent zinc–copper or sodium amalgam reduction was used to prepare the corresponding γ-hydroxy-α-amino acids. König extended this chemistry to the partial synthesis of several dipeptide nikkomycins using, for example, the resolution of the ester **5a** via the amide **6**.[5] Recently Weinreb has applied an intramolecular [4 + 2] cycloaddition reaction in an approach to the N-terminal amino acid of nikkomycin B (**1**).[9] Additionally, Emmer et al. have prepared a series of polyoxin–nikkomycin analogues.[10] Herein we report experimental details on the application of α-oximino amide chemistry to stereoselective amino acid synthesis in the nikkomycin area and additionally we wish to correct errors in our preliminary publication.[11]

Results and Discussion

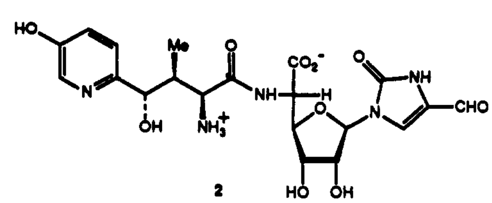
Sequential reaction of 2-oxobutanoic acid with α,α-dichloromethyl methyl ether,[12] *tert*-butylamine in the presence of triethylamine, and hydroxylammonium chloride in methanolic triethylamine gave the oxime **7** (50–78%). This was isolated as a single crystalline geometric isomer, most probably the *Z* on account of hydrogen bonding.[13] Oxime **7** was smoothly converted into the corresponding yellow trianion **17**[14] by reaction with butyllithium in THF–TMEDA at 0 °C (Scheme I), and this was allowed to react with 4-methoxybenzaldehyde to produce the isoxazoline **8** (80%) on acid workup. Although the intermediate aldol product **18a** was obtained as a mixture of isomers, the isoxazoline **8** was isolated as the trans isomer only. Presumably, the cyclization of **18a**, which proceeded via an S_N1 reaction, and cation **19** was

(8) Structures **5** and **7–29** refer to racemic modifications.
(9) Melnick, M. J.; Weinreb, S. M. *J. Org. Chem.* **1988**, *53*, 850.
(10) Emmer, G.; Ryder, N. S.; Grassberger, M. A. *J. Med. Chem.* **1985**, *28*, 278.
(11) For our preliminary studies in this area, see: Banks, B. J.; Barrett, A. G. M.; Russell, M. A.; Williams, D. J. *J. Chem. Soc., Chem. Commun.* **1983**, 873. In this paper the structure of nikkomycin B (1) has the incorrect absolute stereochemistry of the N-terminal amino acid. In 1985, König and co-workers showed that the stereochemistry was 2*S*,3*S*,4*S*; see ref 6.
(12) Ottenheijm, H. C. J.; DeMan, J. H. M. *Synthesis* **1975**, 163.
(13) Bernadou, J.; Fayet, J. P.; Bonnefous, M.; Mauret, P. *Bull. Soc. Chim. Belg.* **1978**, *87*, 747.
(14) For previous studies on oxime anions, see: Henoch, F. E.; Hampton, K. G.; Hauser, C. R. *J. Am. Chem. Soc.* **1969**, *91*, 676. Beam, C. F.; Dyer, M. C. D.; Schwarz, R. A.; Hauser, C. R. *J. Org. Chem.* **1970**, *35*, 1806. Kofron, W. G.; Yeh, M.-K. *Ibid.* **1976**, *41*, 439. Barber, G. N.; Olofson, R. A. *Ibid.* **1978**, *43*, 3015. Lyle, R. E.; Fribush, H. M.; Lyle, G. G.; Saavedra, J. E. *Ibid.* **1978**, *43*, 1275. Jung, M. E.; Blair, P. A.; Lowe, J. A. *Tetrahedron Lett.* **1976**, 1439.

Chart I



1



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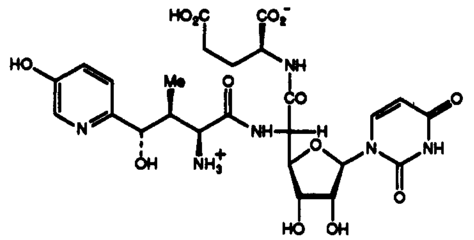
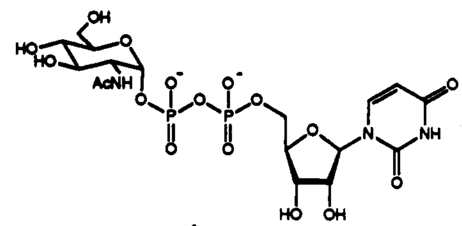
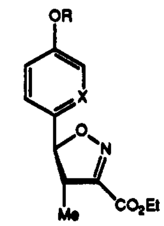


3

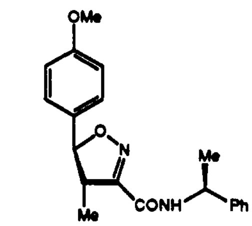


4



5

a X = CH, R = Me
b X = N, R = H

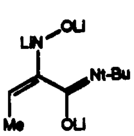


6

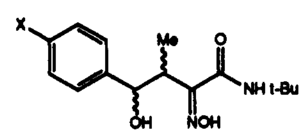
reversible and thereby controlled by thermodynamics (of lactone equilibration, vide infra). Assignment of the stereochemistry of the isoxazoline 8 followed from the ^{1}H NMR spectrum [δ ($CDCl_3$) 5.14 (d, 1 H, J = 8 Hz, 5-H)]. König has reported that the amide 6[6] has comparable coupling constants for the C-4 and C-5 protons [δ ($CDCl_3$) 5.16 (d, 1 H, J = 8 Hz, 5-H)]. Although the intermediate β-hydroxy oxime **18a** was not fully authenticated, the corresponding phenyl compound **18b** was prepared and characterized. Thus reaction of trianion **17** with benzaldehyde gave **18b** (59%). In contrast to oxime **18a**, the phenyl analogue was not readily cyclized to produce the corresponding isoxazoline. This is not surprising since the intermediate cation corresponding to **19** would be less easily formed.

Reduction of the isoxazoline 8 using Red-Al (sodium bis(2-methoxyethoxy)aluminum hydride, Aldrich) followed by benzoylation gave the benzamides 9 (78%) and 10 (5%). The structure of the major isomer was determined to have the nikkomycin B relative stereochemistry from an X-ray crystallographic study.[11] This is a most surprising stereochemical result. On the basis of extensive elegant studies by Jäger,[15] we expected that the major isomer would indeed be 10 rather than 9. Such an expectation follows from steric approach controlled reduction of 8 to give the corresponding isoxazolidine followed by reductive N–O cleavage. In this analysis, the bulky 4-methoxyphenyl group controls the initial hydride attack. However, in the isoxazoline 8, the amide functionality must certainly perturb the isoxazoline ring and weaken the N–O bond. Thus we favor initial N–O cleavage and subsequent reduction of the imine group. Thus the stereochemistry of reduction is controlled since the transition state **20** is sterically congested and **21** is thereby lower in energy

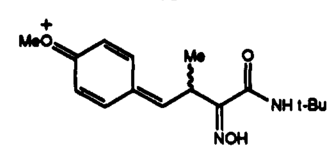
Chart II



17

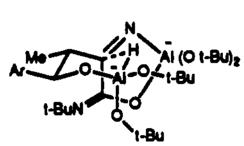


18

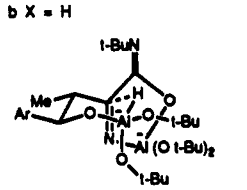


19

a X = OMe
b X = H



20



21

Ar = 4-$MeOC_6H_4$

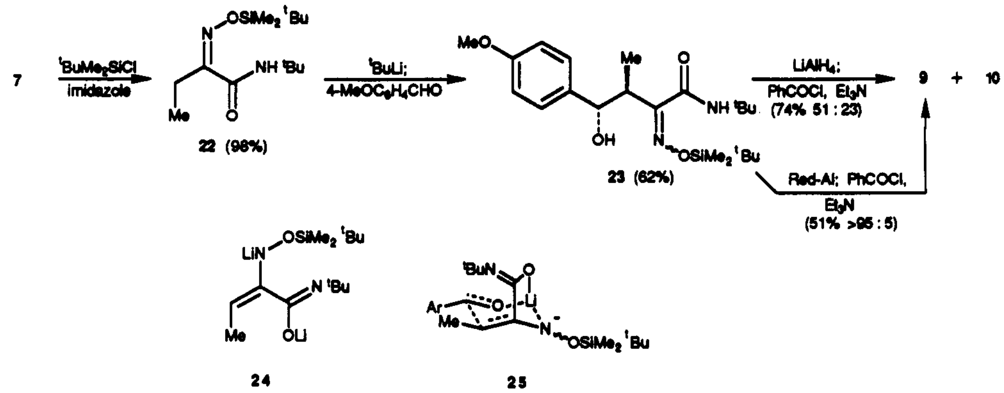
(Chart II). There is indirect precedent for early N–O cleavage in the reductions of isoxazolines. Wang and Sukenik[16] have shown that the reduction of oximes using lithium aluminum hydride in THF and HMPA proceed via the intermediacy of imines. Isoxazoline 8 was also reduced by using lithium aluminum hydride and lithium di-*tert*-butoxyaluminum hydride[17] to give, on benzoylation,

(15) For example, see: Jäger, V.; Buss, V.; Schwab, W. *Liebigs Ann. Chem.* **1980**, 122.

(16) Wang, S.-S.; Sukenik, C. N. *J. Org. Chem.* **1985**, *50*, 5448. Balachander, N.; Wang, S.-S.; Sukenik, C. N. *Tetrahedron Lett.* **1986**, *27*, 4849.

(17) Horne, D. A. *J. Am. Chem. Soc.* **1980**, *102*, 6011.

Scheme II



the amides **9** (67%, 81%) and **10** (31%, 4%) respectively. Reduction using lithium aluminum hydride and diethylaluminum chloride followed by benzoylation gave the amides **9** (38%) and **10** (56%). It is possible that reduction under these Lewis acidic conditions involved a change of mechanism.

There is of course the possibility, albeit unlikely, that amides **9** and **10** were interconverting during their preparation and that the isolated ratio was not the result of kinetic selectivity. In order to refute this possibility, the isoxazoline **8** was reduced with Red-Al and the intermediate amino amide **11** isolated by recrystallization (47%). The ^{1}H NMR spectrum of this substance was fully consistent with the assigned stereochemistry [δ ($CDCl_3$) 4.43 (d, 1 H, J = 7.2 Hz, 4-H), 3.48 (d, 1 H, J = 2.8 Hz, 2-H)]. These two J values are consistent with H-2 being cis to H-3 and trans to H-4 in the cyclic hydrogen-bonded[7] (OH, NH_2) amide **11**. Additionally, the ^{1}H NMR spectrum of crude **11** prior to recrystallization was consistent with the presence of **11** as the major component. Finally, saponification[6] of amide **11** gave the corresponding amino acid **12**, which was isolated at pH 5.5. The material (mp 217–218 °C dec) showed ^{1}H and ^{13}C NMR spectra in reasonable agreement with data reported by Jäger and Franz[7] for this racemic substance.

Alternatively, saponification of amide **11** followed by acidification using hydrochloric acid gave the lactone hydrochloride **13** (X = Cl) (81%). This product (mp 243 °C) showed ^{1}H and ^{13}C NMR spectra in excellent agreement with the data reported by Jäger and Franz for this racemic substance.[7] In our original communication, [11] we reported that reduction of isoxazoline **8** and hydrolysis using hydrochloric acid gave amino acid **11**. This is incorrect since the product is in fact the lactone hydrochloride **13** (X = Cl). In the same way reduction of the isoxazoline **8** using Red-Al followed by hydrolysis using trifluoroacetic acid gave the corresponding lactone **13**, which was most conveniently isolated as the hydrogen 4-toluenesulfonate salt **13** (X = OTs, 46% overall). The same salt **13** (X = OTs, 75%) was also formed on the acidification of the amino acid **12**. Lactone **13** was readily converted into the amide **14**[7] (78%) and carbamate **15** (64%). Finally, reaction of the amino amide **11** with hydrogen bromide in acetic acid resulted in clean de-O-methylation and de-*tert*-butylation to produce the corresponding lactam hydrobromide **16** (100%). In our original communication we incorrectly reported that this reaction gave rise to the corresponding amino acid (see Scheme III).

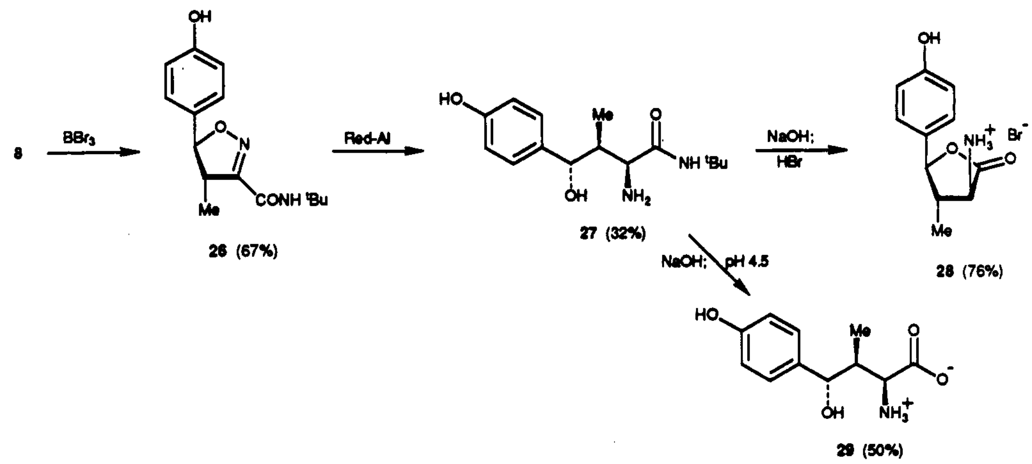
It is clear from all these results that stereochemical control in the synthesis of amino acid **12** is the result of a kinetic preference on the reduction of the isoxazoline **8**. Jäger has reported an alternative method to control stereochemistry. Thus his group has shown, by acid-catalyzed equilibration, that the lactone **13** (X = Cl) is thermodynamically more stable than ring epimers.[7] Additionally, this group has demonstrated the facile interconversion of such lactones under acidic conditions. Notwithstanding these observations, it is still clear that stereochemical control in our approach has a kinetic rather than thermodynamic basis.

In parallel with the oxime trianion chemistry, we also examined the corresponding *O*-silyl oxime **22** and its derived dianion **24** (Scheme II). Silylation of oxime **7** gave the corresponding *O*-silyl derivative in excellent yield as a single geometric isomer. This was tentatively assigned the *Z* geometry and was assumed to arise via silylation with retention of stereochemistry. Oxime **22** was readily converted into the corresponding dianion **24** by using butyllithium in THF and TMEDA. Addition of 4-methoxybenzaldehyde gave the corresponding adduct **23** (62%) as a mixture of two isomers. Recrystallization gave a single compound. Reduction of the crude oximino amides **23** using lithium aluminum hydride and benzoylation gave the benzamides **9** (51%) and **10** (23%). Alternatively, reduction using Red-Al followed by benzoylation gave only the amide **9** (51%). It is reasonable, on the basis of these observations, to state that the oxime **23** was diastereoisomerically pure but contained both oxime geometric isomers. Presumably, stereochemical control resulted from the *E* dianion **24** reacting with 4-methoxybenzaldehyde via the transition state **25**.

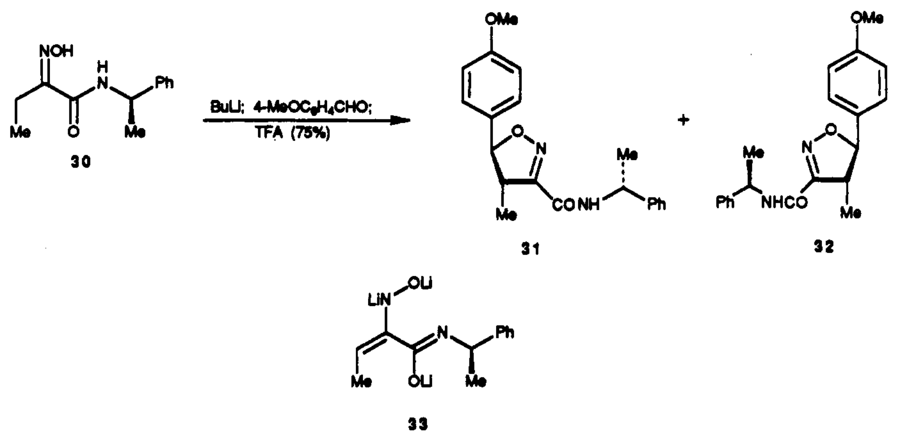
Following the König precedent for related molecules,[6] the isoxazoline was cleanly de-O-methylated by using boron tribromide to provide the phenol **26** (67%) (Scheme III). This was smoothly reduced to provide the corresponding amine **27**, which was isolated in modest yield by recrystallization. Again the assignment of stereochemistry was consistent with the J values in the ^{1}H NMR spectrum [δ ($CDCl_3$) 4.29 (d, 1 H, J = 8.8 Hz, 4-H), 3.61 (d, 1 H, J = 2.8 Hz, 2-H)]. Additionally, saponification of amide **27** followed by acidification with methanolic hydrogen bromide gave the lactone hydrobromide **28**. Again stereochemistry was assigned on the basis of J values in the ^{1}H NMR spectrum [δ (D_2O) 5.11 (d, 1 H, J = 10.4 Hz, 5-H), 4.23 (d, 1 H, J = 12 Hz, 3-H)]. Alternatively, saponification of the amide **27** and careful acidification to pH 4.4 gave the crystalline amino acid **29** (50%). The ^{1}H NMR spectroscopic data for this substances were in reasonable agreement with data published by König for an optically pure synthetic sample of the N-terminal amino acid of nikkomycin B (**29**).

Finally, we have adapted our α-oximino amide trianion chemistry to prepare optically pure isoxazoline **31** (Scheme IV). Oxime **30** (68%) was easily prepared from 2-oxobutanoic acid and (*R*)-α-methylbenzylamine. Metalation using butyllithium in THF and TMEDA and addition of

Scheme III



Scheme IV



4-methoxybenzaldehyde gave, on acidification, the diastereoisomeric isoxazolines **31** and **32** (75%). Recrystallization gave the diastereoisomerically pure isoxazoline **31** [mp 123 °C, $[\alpha]_D$ +294° (*c* 1.01, $CHCl_3$)]. Data for this substance were in agreement with that reported by König for the enantiomer.[6] König has employed the antipode of isoxazoline **32** in the synthesis of the optically pure nikkomycin B N-terminal amino acid (**29**).

Conclusion

These results establish that the α-oximino amide trianions **17** and **33** and the related dianion **24** are useful intermediates for the stereoselective synthesis of γ-hydroxy-α-amino acids. Additionally, our results show that the hydride reduction of the isoxazoline-2-carboxamides **8** and **26** probably proceed via early N–O cleavage and intramolecular imine reduction.

Experimental Section

General Procedures. Reactions were carried out under dry N_2 at room temperatures unless otherwise stated. Low reaction temperatures were recorded as bath temperatures. Column chromatography was performed with E. Merck silica gel 60, 230–400 mesh ASTM. Analytical thin layer chromatography (TLC) was performed on E. Merck pre-coated silica gel 60 F_{254} plates. Hexanes (ACS reagent boiling range 35–60 °C), EtOAc, CH_2Cl_2, and MeOH were purified by distillation. THF, Et_2O, and hexanes were dried by distillation from Na (or K)/benzophenone ketyl. CH_2Cl_2 was dried by distillation from CaH_2 and stored over 4-Å molecular sieves. DMF was dried by distillation at reduced pressure from CaH_2 or BaO and stored over 4-Å molecular sieves. TMEDA was dried by distillation from Na wire or KOH and stored over KOH. Et_3N was dried by distillation from Na wire or CaH_2 and stored over KOH or 4-Å molecular sieves. All other reagents were used as supplied unless otherwise noted.

***N-tert*-Butyl-2-(hydroxyimino)butanamide (7).** To 2-oxobutanoic acid (25 g) was added over 30 min α,α-dichloromethyl methyl ether (28 g). The mixture was warmed to 60 °C for 30 min by which time HCl gas evolution had ceased. The reaction mixture was cooled at 25 °C, diluted with CH_2Cl_2 (250 mL), and further cooled to −78 °C. A solution of *tert*-butylamine (25.9 mL) and Et_3N (34.4 mL) in CH_2Cl_2 (50 mL) was added over 30 min, and the reaction mixture allowed to warm to 25 °C and poured into H_2O (250 mL). The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (125 mL). The combined organic layers were washed with HCl (2 M; 2 × 125 mL) and saturated aqueous $NaHCO_3$ (2 × 125 mL), dried ($MgSO_4$), and evaporated. The residue was dissolved in MeOH (200 mL) and hydroxylamine hydrochloride (25.5 g) added followed by Et_3N (51.0 mL). The reaction mixture was warmed to 70 °C for 30 min, allowed to cool, and evaporated to dryness. The residue was suspended in CH_2Cl (125 mL), washed with H_2O (125 mL), HCl (2 M; 125 mL), and saturated aqueous $NaHCO_3$ (125 mL), dried ($MgSO_4$), and evaporated. The residue was crystallized (Et_2O/hexanes) to give the oxime **7** (20.23 g, 50%) as colorless crystals: mp 109 °C (Et_2O/hexanes); IR (Nujol) 3384, 3260, 1665, 1638, 1528, 908 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 8.25 (br s, 1 H), 6.50 (br s, 1 H), 2.55 (q, 2 H, J = 7 Hz), 1.40 (s, 9 H), 1.05 (t, 3 H, J = 7 Hz); MS (EI) *m/e* 172 ($M^{•+}$) 157. Anal. Calcd for $C_8H_{16}N_2O_2$: C, 55.79; H, 9.36; N, 16.27. Found: C, 55.69; H, 9.52; N, 16.21. On a smaller scale, reaction of 2-oxobutanoic acid (4.16 g) with $MeOCHCl_2$, *t*-$BuNH_2$, and $NH_2OH·HCl$ in CH_2Cl_2 gave the oxime (5.45 g, 78%).

[5(*S*,*R*),4(*S*,*R*)]-5-(4-Methoxyphenyl)-4-methyl-*N-tert*-butylisoxazolinecarboxamide (8). To a solution of the oxime **7** (1.72 g) in anhydrous THF (200 mL) at −78 °C was added *n*-BuLi

(1.5 M; 21 mL) followed by TMEDA (5.16 mL). The reaction mixture was allowed to warm up to 0 °C, maintained for 30 min, then recooled to −78 °C, and quenched with 4-methoxybenzaldehyde (freshly distilled; 1.4 g) followed by HOAc (8 mL). The reaction mixture was evaporated and the residue suspended in Et_2O (250 mL), washed with H_2O (2 × 100 mL), dried (Na_2SO_4), and evaporated. The residue was dissolved in anhydrous CH_2Cl_2 (30 mL) and trifluoroacetic acid (1 mL) added. After 1 h, the mixture was evaporated and the residue purified by chromatography on silica (CH_2Cl_2) to give the isoxazoline **8** (2.31 g, 80%) as a white crystalline solid: mp 98–99 °C (MeOH); IR (Nujol) 3318, 1662, 1614, 1588, 1514, 1258, 1219, 1188, 1033, 918, 810 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.23, 6.90 (AB q, 4 H, J = 8.8 Hz), 6.51 (br s, 1 H), 5.14 (d, 1 H, J = 8 Hz), 3.81 (s, 3 H), 3.54 (m, 1 H), 1.45 (d, 3 H, J = 6.8 Hz), 1.41 (s, 9 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.8, 158.8, 157.4, 131.3, 127.3, 114.2, 92.03, 55.30, 51.72, 49.5, 28.7, 17.2; MS (EI) m/e 290 ($M^{•+}$), 273, 234, 217. Anal. Calcd for $C_{16}H_{22}N_2O_3$: C, 66.19; H, 7.64; N, 9.65. Found: C, 66.18; H, 7.77; N, 9.64.

2-(Hydroxyimino)-4-hydroxy-3-methyl-4-phenyl-*N*-*tert*-butylbutanamide (18b). The oxime **7** (172 mg) in anhydrous THF (8 mL) was converted to the trianion[17] as previously described. The reaction mixture was quenched at −78 °C with PhCHO (0.075 mL) followed by HOAc (0.8 mL). The reaction mixture was evaporated, and the residue was dissolved in Et_2O (50 mL), extracted with H_2O (20 mL), and dried (Na_2SO_4). Evaporation and purification of the residue by chromatography on silica (CH_2Cl_2/Et_2O gradient) afforded the oximino amide **18b** (120 mg, 59%): mp 134–139 °C (Et_2O/hexanes); IR (Nujol) 3400, 3280, 3220, 1650, 1630, 1560, 1530, 1380, 1343, 1223, 1020, 985 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 7.2 (m, 5 H), 6.6 (s, 1 H), 4.95 (m, 1 H), 3.78 (m, 1 H), 1.34, 1.30 (2 s, 9 H), 1.2, 1.1 (2 d, 3 H, J = 7 Hz); MS (EI) m/e 261 ($M^{•+}$ − OH), 260, 245, 244, 172, 156. Anal. Calcd for $C_{15}H_{22}N_2O_3$: C, 64.73; H, 7.97; N, 10.06. Found: C, 64.62; H, 8.22; N, 9.98.

[2(*S*,*R*),3(*S*,*R*),4(*S*,*R*)]-2-Benzamido-4-hydroxy-4-(4-methoxyphenyl)-3-methyl-*N*-*tert*-butylbutanamide (9 and 10). To the isoxazoline **8** (200 mg) in anhydrous THF (6 mL) at −78 °C was added Red-Al (70% v/v in toluene; 2 mL). The mixture was allowed to warm up to 25 °C and maintained for 24 h, recooled to −78 °C, quenched with saturated aqueous K_2CO_3, and extracted with EtOAc (130 mL). The extract was dried (Na_2SO_4) and evaporated, and the residue was dissolved in anhydrous CH_2Cl_2 (30 mL). To the solution at 0 °C was added Et_3N (200 mg) followed by PhCOCl (100 mg), and the mixture was allowed to warm up to 25 °C and stirred for 6 h. After evaporation, the residue was redissolved in Et_2O (100 mL) and washed with HCl (2 M; 2 × 25 mL) and H_2O (2 × 30 mL), dried (Na_2SO_4), and evaporated. Chromatography of the residue on silica (9:1 CH_2Cl_2/Et_2O) gave, in order of increasing polarity, the benzamido amides **9** (215 mg, 78%) and **10** (14 mg, 5%). The major isomer **9** was obtained as a white crystalline solid: mp 177.5–178 °C (MeOH); IR (Nujol) 3280 (br), 1670, 1620, 1522, 1302, 1030, 844 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.93 (m, 2 H), 7.54 (m, 4 H), 7.30, 6.88 (AB q, 4 H, J = 8 Hz), 6.08 (s, 1 H), 5.90 (d, 1 H, J = 4 Hz), 5.06 (dd, 1 H, J = 7.5, 2.5 Hz), 4.21 (dd, 1 H, J = 10, 4 Hz), 3.80 (s, 3 H), 2.21 (ddq, 1 H, J = 10, 2.5, 7 Hz), 1.33 (s, 9 H), 0.64 (d, 3 H, J = 7 Hz); MS (EI) m/e 398 ($M^{•+}$), 381, 380, 281. Anal. Calcd for $C_{23}H_{30}N_2O_4$: C, 69.32; H, 7.59; N, 7.03. Found: C, 69.07; H, 7.53; N, 6.99. This structure of isomer **9** was confirmed by an X-ray crystrallographic study.[11] The minor isomer **10** was obtained as a white crystalline solid: mp 175–176 °C (MeOH); IR (Nujol) 3380, 3300, 1670, 1640, 1511, 1256, 1024, 832 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.82 (m, 2 H), 7.45 (m, 4 H), 7.34, 6.88 (AB q, 4 H, J = 8 Hz), 6.79 (s, 1 H), 5.02 (dd, 1 H, J = 7, 4.2 Hz), 4.36 (dd, 1 H, J = 9.6, 6 Hz), 3.80 (s, 3 H), 3.60 (d, 1 H, J = 6 Hz), 2.65 (ddq, 1 H, J = 9.6, 4.2, 7 Hz), 1.42 (s, 9 H), 0.75 (d, 3 H, J = 7 Hz); MS (EI) m/e 380 ($M^{•+}$ − H_2O), 280, 234. Anal. Calcd for $C_{23}H_{30}N_2O_4$: C, 69.32; H, 7.59; N, 7.03. Found: C, 69.33; H, 7.67; N, 6.98.

The two isomers **9** and **10** were also produced by using alternative reducing agents in the following isolated yields: (1) $LiAlH_4$ **9** (67%) and **10** (31%); (2) Et_2AlCl–$LiAlH_4$ **9** (38%) and **10** (56%); (3) $LiAlH_2(O\text{-}t\text{-}Bu)_2$ **9** (81%) and **10** (4%).

In all of these experiments, the ratios of the two benzamido amides were identical with the ratios of the crude amines prior to benzoylation (^1H NMR spectra).

[2(*S*,*R*),3(*S*,*R*),4(*S*,*R*)]-2-Amino-4-hydroxy-4-(4-methoxyphenyl)-3-methyl-*N*-*tert*-butylbutanamide (11). To the isoxazoline **8** (8.0 g) in anhydrous THF (50 mL) at −78 °C was added Red-Al (3.4 M in toluene; 16.3 mL) dropwise. The reaction mixture was maintained at −78 °C for 1 h, warmed to 4 °C, and allowed to stand for 18 h. The reaction mixture was recooled to −78 °C and quenched by the addition of saturated aqueous $NaHSO_4$. Solids were removed by filtration through Celite and the residue was washed with Et_2O. The organic layer was separated, dried ($MgSO_4$), and evaporated to yield the hydroxy amide **11** (3.8 g, 47%) as a white crystalline solid: mp 148–149 °C (EtOH); IR (KBr) 3428, 3320, 2980, 2963, 2919, 2870, 2842, 1652, 1611, 1513, 1460, 1396, 1384, 1369, 1350, 1336, 1288, 1251, 1230, 1178, 1143, 1119, 1104, 1069, 1028, 982, 883, 831, 789, 778, 761, 694, 642, 572, 549, 494, 440 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.22, 6.82 (AB q, 4 H, J = 8 Hz), 6.72 (br s, 1 H), 4.43 (d, 1 H, J = 7.2 Hz), 3.75 (s, 3 H), 3.48 (d, 1 H, J = 2.8 Hz), 2.28 (m, 1 H), 1.28 (s, 9 H), 0.72 (d, 3 H, J = 8 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.7, 158.6, 135.8, 127.3, 113.6, 76.5, 55.2, 54.6, 50.8, 42.4, 28.8, 10.7; MS (EI) m/e 294 ($M^{•+}$), 277, 194, 176, 137. Anal. Calcd for $C_{16}H_{26}N_2O_3$: C, 65.28; H, 8.90; N, 9.52. Found: C, 65.01; H, 9.06; N, 9.60.

[2(*S*,*R*),3(*S*,*R*),4(*S*,*R*)]-2-Amino-4-hydroxy-4-(4-methoxyphenyl)-3-methylbutanoic Acid (12). To the amide **11** (7.0 g) in MeOH (250 mL) was added NaOH (9.3 g) in H_2O (20 mL), and the mixture allowed to react for 48 h. After evaporation, the residue in H_2O (75 mL) was washed with CH_2Cl_2 (75 mL) and *carefully* acidified to pH 5.5 using HCl (2 M). The crystalline amino acid **12** was filtered off and concentration of the mother liquors afforded additional material, together giving the desired amino acid **12** (3.7 g, 65%): mp 217–218 °C dec (H_2O) (lit.[7] mp 209–211 °C); IR (KBr) 3208, 3000–2400 (br), 1600, 1502, 1391, 1350, 1303, 1272, 1247, 1172, 1083, 1028, 835, 810, 768, 722, 644, 590 cm^{-1}; ^1H NMR (400 MHz, D_2O/NaOD) δ 7.21, 6.86 (AB q, 4 H, J = 8 Hz), 4.42 (d, 1 H, J = 7.6 Hz), 3.63 (s, 3 H), 3.52 (d, 1 H, J = 2.8 Hz), 2.18 (m, 1 H), 0.67 (d, 3 H, J = 7.2 Hz); ^{13}C NMR (101 MHz, D_2O/NaOD) δ 185.1, 160.7, 138.2, 130.7, 116.5, 78.2, 58.1, 56.9, 44.9, 12.8; MS (FAB) m/e 222 (M^+ − OH), 207, 199, 185, 167, 149, 131, 117, 107; exact mass (FAB) calcd for $C_{12}H_{16}NO_3$ (M^+ − OH), 222.1131, found (M^+ − OH), 222.1128. Anal. Calcd for $C_{12}H_{17}NO_4$: C, 60.24; H, 7.16; N, 5.85. Found: C, 59.86; H, 7.28; N, 5.71.

[3(*S*,*R*),4(*S*,*R*),5(*S*,*R*)]-3-Amino-5-(4-methoxyphenyl)-4-methyltetrahydrofuran-2-one Hydrochloride (13, X = Cl). To the amide **11** (2.2 g) in MeOH (60 mL) was added NaOH (3.0 g) in H_2O (6 mL), and the solution was stirred for 48 h. The solution was diluted with H_2O and acidified to pH 1 with concentrated HCl. This afforded a white crystalline solid, which was collected by filtration and dried to give the lactone **13** (X = Cl) (1.57 g, 81%): mp 243 °C (MeOH/H_2O) (lit.[7] mp 245–246 °C); IR (KBr) 3200–2400, 1775, 1600, 1560, 1492, 1370, 1328, 1279, 1242, 1192, 1168, 1060, 1020, 980, 827, 766 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 9.23 (br s, 3 H), 7.44, 7.00 (AB q, 4 H, J = 8 Hz), 5.12 (d, 1 H, J = 10 Hz), 4.28 (d, 1 H, J = 10.8 Hz), 3.83 (s, 3 H), 2.87 (m, 1 H), 1.17 (d, 3 H, J = 6.6 Hz); ^1H NMR (400 MHz, D_2O) δ 7.50, 7.11 (AB q, 4 H, J = 8 Hz), 5.25 (d, 1 H, J = 10.8 Hz), 4.36 (d, 1 H, J = 11.2 Hz), 3.87 (s, 3 H), 2.85 (m, 1 H), 1.24 (d, 3 H, J = 6 Hz); ^{13}C NMR (101 MHz, D_2O) δ 175.3, 162.5, 131.5, 129.6, 116.9, 88.6, 58.2, 58.0, 46.0, 14.5; ^{13}C NMR (101 MHz, DMSO-d_6) δ 171.7, 159.7, 128.9, 127.9, 114.0, 84.6, 55.2, 54.7, 42.7, 12.7; MS (EI) m/e 257 ($M^{•+}$), 234, 221, 177, 162, 145, 135, 121; exact mass (FAB) calcd for $C_{12}H_{16}NO_3$ [(M^+ + H) − HCl], 222.1131, found [(M^+ + H) − HCl], 222.1123. Anal. Calcd for $C_{12}H_{16}ClNO_3$: C, 55.93; H, 6.26; N, 5.44. Found: C, 55.52; H, 6.27; N, 5.33.

[3(*S*,*R*),4(*S*,*R*),5(*S*,*R*)]-3-Amino-5-(4-methoxyphenyl)-4-methyltetrahydrofuran-2-one Hydrogen 4-Toluenesulfonate (13, X = OTs). (1) To a stirred solution of the isoxazoline **8** (3.0 g) in THF (15 mL) at −78 °C was added Red-Al (3.4 M in toluene; 6.68 mL). The reaction mixture was stirred for 18 h at 4 °C, quenched with saturated aqueous $NaHSO_4$ (10 mL), and extracted with $CHCl_3$ (200 mL). The extract was dried (Na_2SO_4) and reduced in volume to 80 mL, and trifluoroacetic acid (1.58 mL) was added. After allowing the reaction to reflux for 18 h, the solution was neutralized with saturated aqueous $NaHCO_3$ (30 mL), and the organic phase was separated, dried (Na_2SO_4), and evaporated. The residue was dissolved in MeOH (120 mL), to which a methanolic solution of 4-toluenesulfonic acid (2.0 g) was added. Dilution with Et_2O gave the lactone 13 (X = OTs) (1.70 g, 46%) as a white crystalline compound: mp 231–232 °C ($MeOH/Et_2O$); IR (Nujol) 3100 (br), 1780, 1612, 1515, 1289, 1251, 1239, 1211, 1161, 1125, 1040, 1014, 970, 940, 814 cm^{-1}; ^1H NMR (90 MHz, CD_3OD) δ 7.68, 7.40, 7.25, 6.98 (4 d, 8 H, J = 8 Hz), 5.12 (d, 1 H, J = 9 Hz), 4.28 (d, 1 H, J = 11 Hz), 3.82 (s, 3 H), 2.76 (m, 1 H), 2.35 (s, 3 H), 1.23 (d, 3 H, J = 7 Hz); MS (EI) m/e 221 ($M^{\bullet+}$ – TsOH), 177, 162, 145, 121, 107. Anal. Calcd for $C_{19}H_{23}NO_6S$: C, 58.00; H, 5.89; N, 3.56. Found: C, 57.90; H, 5.95; N, 3.34.

(2) To the amino acid 12 (3.0 g) in aqueous MeOH (1:1; 30 mL) was added trifluoroacetic acid (9.7 mL). After 24 h, the reaction was poured into saturated aqueous $NaHCO_3$ (100 mL) and extracted with CH_2Cl_2 (2 × 50 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. The residue was dissolved in MeOH (5 mL) and a solution of 4-toluenesulfonic acid (3.6 g) in MeOH (5 mL) added. After 5 min, the product was precipitated by the addition of Et_2O and isolated by filtration to yield the lactone 13 (X = OTs) (3.64 g, 75%): mp 230 °C ($MeOH/Et_2O$). The spectral data were in agreement with that previously cited for this compound.

[3(*S*,*R*),4(*S*,*R*),5(*S*,*R*)]-3-Acetamido-5-(4-methoxyphenyl)-4-methyltetrahydrofuran-2-one (14). To a stirred solution of the lactone hydrochloride 13 (X = Cl) (30 mg) in pyridine (2 mL) at 0 °C was added Ac_2O (0.5 mL) over 15 min. The reaction mixture was allowed to warm to 25 °C and maintained for 2 h, quenched by the addition of cold HCl (2 M; 40 mL), and extracted with CH_2Cl_2 (2 × 25 mL). The combined organic extracts were washed with HCl (1 M; 2 × 20 mL), saturated aqueous $NaHCO_3$ (2 × 20 mL), and brine (20 mL), dried (Na_2SO_4), and evaporated to give the lactone 14 (24 mg, 78%) as a crystalline solid: mp 126–128 °C (CH_2Cl_2/Et_2O) (lit.[7] mp 123–132 °C); IR (Nujol) 3380, 1760, 1675, 1615, 1585, 1515, 1331, 1311, 1258, 1229, 1180, 1131, 1032, 972, 938, 830 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 7.35, 6.93 (AB q, 4 H, J = 8 Hz), 6.50 (br d, 1 H, J = 8 Hz), 4.90 (d, 1 H, J = 11 Hz), 4.63 (dd, 1 H, J = 11, 9 Hz), 3.80 (s, 3 H), 2.50 (m, 1 H), 2.08 (s, 3 H), 1.15 (d, 3 H, J = 7 Hz); MS (EI) m/e 263 ($M^{\bullet+}$), 176, 160, 145, 135, 121. Anal. Calcd for $C_{14}H_{17}NO_4$: C, 63.87; H, 6.51. Found: C, 63.88; H, 6.48.

[3(*S*,*R*),4(*S*,*R*),5(*S*,*R*)]-5-(4-Methoxyphenyl)-4-methyl-3-[[[2-(trimethylsilyl)ethoxy]carbonyl]amino]tetrahydrofuran-2-one (15). To a stirred suspension of the tosylate lactone 13 (X = OTs) (7.29 g) and 2-(trimethylsilyl)ethyl 4-nitrophenyl carbonate (8.1 g) in anhydrous THF (35 mL) was added Et_3N (5.6 g). The solution was stirred at 25 °C for 48 h, diluted with Et_2O (50 mL), and poured into H_2O (50 mL). The organic layer was separated and the aqueous layer extracted with Et_2O (50 mL). The combined organic layers were washed with cold NaOH (1 M; 50 mL), dried ($MgSO_4$), and evaporated. Chromatography of the residue on silica (3:7 EtOAc/hexanes) and crystallization of the pale oil from Et_2O/hexanes afforded the lactone 15 (4.35 g, 64%) as colorless prisms: mp 86–87 °C (Et_2O/hexanes); IR (Et_2O) 3320, 2978, 2864, 1790, 1720, 1615, 1518, 1460, 1384, 1319, 1253, 1178, 1121, 1040, 860, 848 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 7.28, 6.88 (AB q, 4 H, J = 8 Hz), 5.20 (br d, 1 H, J = 8 Hz), 4.80 (d, 1 H, J = 11 Hz), 4.18 (m, 3 H), 3.77 (s, 3 H), 2.37 (m, 1 H), 1.15 (d, 3 H, J = 7 Hz), 0.95 (m, 2 H), 0.01 (m, 9 H); MS (EI) m/e 365 ($M^{\bullet+}$), 234, 176, 160, 148, 130, 101. Anal. Calcd for $C_{18}H_{27}NO_5Si$: C, 59.18; H, 7.40; N, 3.83. Found: C, 59.01; H, 7.44; N, 3.82.

[3(*S*,*R*),4(*S*,*R*),5(*S*,*R*)]-3-Amino-5-(4-hydroxyphenyl)-4-methyl-2-pyrrolidinone Hydrobromide (16). The amide 11 (40 mg) was dissolved in HBr (30 wt % in HOAc; 3 mL) and allowed to reflux for 20 h, cooled, and evaporated. The residue was dissolved in H_2O and azeotroped with EtOH (3 × 2 mL) to yield crude lactam 16 (39 mg, 100%) as a brownish red solid. Recrystallization (EtOH) gave material with the following data: mp 269–273 °C dec; IR (KBr) 3401, 3299, 3180, 1713, 1602, 1516, 1348, 1250, 1182, 1169, 847 cm^{-1}; ^1H NMR (400 MHz, D_2O) δ 7.12, 6.74 (AB q, 4 H, J = 8.4 Hz), 4.15 (d, 1 H, J = 8.8 Hz), 3.80 (d, 1 H, J = 10.8 Hz), 2.14 (m, 1 H), 1.01 (d, 3 H, J = 6.4 Hz); ^{13}C NMR (101 MHz, D_2O) δ 172.3, 156.0, 130.3, 128.6, 115.8, 61.9, 57.1, 45.4, 12.7; MS (EI) m/e 206 ($M^{\bullet+}$ – HBr), 189, 148, 134, 122; exact mass (EI) calcd for $C_{11}H_{14}N_2O_2$ ($M^{\bullet+}$ – HBr), 206.1055, found ($M^{\bullet+}$ – HBr), 206.1048. Anal. Calcd for $C_{11}H_{15}BrN_2O_2{\cdot}H_2O$: C, 43.44; H, 5.30; N, 9.21. Found: C, 43.13; H, 5.07; N, 8.99.

***N*-*tert*-Butyl-2-[[(*tert*-butyldimethylsilyl)oxy]imino]butanamide (22).** To a stirred solution of the oxime 7 (1.0 g) in DMF (1.5 mL) were added imidazole (1.0 g) and *tert*-butylchlorodimethylsilane (0.9 g). The reaction mixture was allowed to stir for 18 h, poured into H_2O (150 mL), and extracted with Et_2O (2 × 50 mL). The combined organic layers were dried (Na_2SO_4) and evaporated to give a yellow oil. Purification of the residue by chromatography on silica (4:1 CH_2Cl_2/hexanes) gave the silyl oxime 22 (1.63 g, 98%) as a colorless oil: IR (neat) 1660, 1610, 1560 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 6.55 (br s, 1 H), 2.55 (q, 2 H, J = 7 Hz), 1.35 (s, 9 H), 1.00 (t, 3 H, J = 7 Hz), 0.95 (s, 9 H), 0.20 (s, 6 H); MS (EI) m/e 271 ($M^{\bullet+}$ – Me), 229. Anal. Calcd for $C_{14}H_{30}N_2O_2Si$: C, 58.70; H, 10.55; N, 9.78. Found: C, 58.76; H, 10.72; N, 9.62.

[3(*S*,*R*),4(*S*,*R*)]-2-[[(*tert*-Butyldimethylsilyl)oxy]imino]-4-hydroxy-4-(4-methoxyphenyl)-3-methyl-*N*-*tert*-butylbutanamide (23). To a stirred solution of the butanamide 22 (870 mg) in anhydrous THF (30 mL) at –78 °C was added TMEDA (5 mL) followed by *t*-BuLi (1.1 M in pentane; 6.65 mL). The reaction mixture was allowed to stir at –78 °C for 1.5 h, and 4-methoxybenzaldehyde (0.5 mL) was added followed by HOAc (2.2 mL). The solution was evaporated and the residue extracted with Et_2O (3 × 50 mL). The combined organic layers were washed with H_2O (2 × 200 mL), dried (Na_2SO_4), and evaporated. Purification of the residue by chromatography on silica (1:1 CH_2Cl_2/hexanes) afforded the silyl oximino amide 23 (800 mg, 62%) as a syn–anti mixture. Recrystallization (hexanes) gave a single isomer: mp 108–109 °C; IR (Nujol) 3335, 3250, 1640, 1610, 1555, 1510, 1250, 1035, 960, 870, 845, 790 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33, 6.86 (AB q, 4 H, J = 7 Hz), 6.42 (s, 1 H), 4.96 (d, 1 H, J = 4 Hz), 3.80 (s, 3 H), 1.60 (br s, 1 H), 1.37 (s, 9 H), 1.08 (d, 3 H, J = 7 Hz), 0.98 (s, 9 H), 0.21 (s, 6 H); MS (EI) m/e 422 ($M^{\bullet+}$), 407, 286, 229, 173, 135. Anal. Calcd for $C_{22}H_{38}N_2O_4Si$: C, 62.52; H, 9.06; N, 6.63. Found: C, 62.32; H, 9.13; N, 6.58.

[2(*S*,*R*),3(*S*,*R*),4(*S*,*R*)]-2-Benzamido-4-hydroxy-4-(4-methoxyphenyl)-3-methyl-*N*-*tert*-butylbutanamide (9). (1) To a solution of crude oximino amide 23 (300 mg) in anhydrous THF (4 mL) at –78 °C was added $LiAlH_4$ (150 mg). The reaction mixture was allowed to warm up to 25 °C and maintained for 12 h. The mixture was recooled to –78 °C, quenched with aqueous K_2CO_3, and extracted with EtOAc (10 × 10 mL). The combined extracts were dried (Na_2SO_4) and evaporated and the residue was dissolved in CH_2Cl_2 (10 mL) to which Et_3N (300 mg) and PhCOCl (100 mg) were added. After 12 h, the reaction mixture was evaporated, extracted with Et_2O (150 mL), washed with H_2O (2 × 70 mL), dried (Na_2SO_4), and evaporated. Chromatography of the residue on silica (9:1 CH_2Cl_2/Et_2O) afforded the benzamido amides 9 (144 mg, 51%) and 10 (66 mg, 23%). Spectral data were in agreement with that previously reported.

(2) Reduction of oximino amide (200 mg) using Red-Al and benzoylation gave only the benzamido amide 9 (98 mg, 51%).

[4(*S*,*R*),5(*S*,*R*)]-5-(4-Hydroxyphenyl)-4-methyl-*N*-*tert*-butylisoxazolecarboxamide (26). To the isoxazoline 8 (3.04 g) in anhydrous CH_2Cl_2 (60 mL) at –78 °C was added BBr_3 (1 M in CH_2Cl_2; 32.5 mL) dropwise. The mixture was maintained at –78 °C for 30 min and quenched with H_2O (120 mL). After stirring for 15 min at 25 °C, the solids were removed by filtration through Celite, and the residue was washed with CH_2Cl_2. The organic layer was separated, dried ($MgSO_4$) and evaporated. Chromatography of the residue on silica (3:7 EtOAc/hexanes) and recrystallization from CH_2Cl_2/hexanes gave the phenol 26 (1.93 g, 67%) as a white crystalline solid: mp 145 °C (CH_2Cl_2/hexanes); IR (KBr) 3250 (br), 2961, 2920, 1640, 1608, 1588, 1570, 1534, 1504, 1435, 1358, 1322, 1259, 1214, 1163, 1099, 1084, 1068, 909, 853, 847, 819 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.10, 6.78 (AB q, 4 H, J = 8 Hz), 6.72 (s, 1 H), 6.60 (s, 1 H), 5.11 (d, 1 H, J = 7.2 Hz), 3.50 (dq, 1 H, J = 7.2 Hz), 1.41 (s, d, 12 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.0, 157.2, 156.3, 130.8, 127.3, 115.6, 92.2, 52.1, 49.3, 28.8, 17.4; MS (EI) m/e 276 ($M^{\bullet+}$), 220, 203, 172, 158, 134; exact mass (EI) calcd for $C_{15}H_{20}N_2O_3$ ($M^{\bullet+}$), 276.1475, found ($M^{\bullet+}$), 276.1467. Anal. Calcd for $C_{15}H_{20}N_2O_3$: C, 65.20; H, 7.29; N, 10.14. Found: C, 65.23; H, 7.46; N, 9.81.

[2(*S*,*R*),3(*S*,*R*),4(*S*,*R*)]-2-Amino-4-hydroxy-4-(4-hydroxyphenyl)-3-methyl-*N*-*tert*-butylbutanamide (27). To the isoxazoline **26** (1.47 g) in anhydrous THF (10 mL) at −78 °C was added dropwise Red-Al (3.4 M in toluene; 4.7 mL). The mixture was stirred at −78 °C for 1 h and warmed to and maintained at 0 °C for 12 h. The mixture was recooled to −78 °C and pH 7 phosphate buffer (1 mL) added. The crude reaction mixture was filtered through Celite and washed with Et_2O, and the organic layer was separated, dried ($MgSO_4$), and evaporated to yield hydroxy amide **27** (0.482 g, 32%) as a white crystalline solid: mp 195–197 °C (EtOH); IR (KBr) 3532, 3378, 2699, 2491, 1647, 1617, 1599, 1537, 1517, 1451, 1388, 1369, 1327, 1260, 1228, 1214, 1169, 1103, 1038, 1021, 996, 935, 910, 832, 778 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 7.07, 6.65 (AB q, 4 H, J = 8.8 Hz), 4.29 (d, 1 H, J = 8.8 Hz), 3.61 (d, 1 H, J = 2.8 Hz), 2.06 (m, 1 H), 1.24 (s, 9 H), 0.47 (d, 3 H, J = 7.2 Hz); ^{13}C NMR (101 MHz, CD_3OD) δ 176.5, 158.0, 135.9, 129.0, 116.0, 76.8, 55.8, 51.8, 44.5, 28.9, 10.6; MS (FAB) m/e 281 (M^+ + H), 263, 180; exact mass calcd for $C_{15}H_{25}N_2O_3$ (M^+ + H), 281.1865, found (M^+ + H), 281.1890. Anal. Calcd for $C_{15}H_{24}N_2O_3 \cdot 0.5H_2O$: C, 62.26; H, 8.71, N, 9.68. Found: C, 62.48; H, 8.84; N, 9.69.

[3(*S*,*R*),4(*S*,*R*),5(*S*,*R*)]-3-Amino-5-(4-hydroxyphenyl)-4-methyltetrahydrofuran-2-one Hydrobromide (28). To the amide **27** (26 mg) in MeOH (0.5 mL) was added NaOH (1 M; 0.5 mL), and the solution was stirred for 48 h. The solution was evaporated, taken up in MeOH (1 mL), and acidified to pH 1 with methanolic HBr. Dilution with Et_2O afforded the lactone **28** (19 mg, 76%) as a white crystalline solid: mp 275–278 °C dec; IR (KBr) 3660, 3596, 3528, 3255, 1796, 1656, 1621, 1518, 1270, 1210, 1186, 1000, 850 cm^{-1}; ^1H NMR (400 MHz, D_2O) δ 7.27, 6.84 (AB q, 4 H, J = 8 Hz), 5.11 (d, 1 H, J = 10.4 Hz), 4.23 (d, 1 H, J = 12 Hz), 2.68 (m, 1 H), 1.08 (d, 3 H, J = 6.4 Hz); MS (EI) m/e 207 ($M^{•+}$ − HBr), 200, 199, 190, 163, 148, 131, 107; exact mass (EI) calcd for $C_{11}H_{13}NO_3$ ($M^{•+}$ − HBr), 207.0895, found ($M^{•+}$ − HBr), 207.0901.

[2(*S*,*R*),3(*S*,*R*),4(*S*,*R*)]-2-Amino-4-hydroxy-4-(4-hydroxyphenyl)-3-methylbutanoic Acid (29). To the amide **27** (26 mg) in EtOH (0.5 mL) was added NaOH (1 M; 0.5 mL). The reaction was allowed to stir for 3 h and evaporated, and the residue was dissolved in H_2O (1 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 1 mL) and *carefully* acidified to pH 4.5 with HCl (0.5 M) to yield the crystalline amino acid **29** (10 mg, 50%): mp 160–162 °C dec (H_2O/EtOH); IR (KBr) 3419 (br), 1620, 1518, 1460, 1383, 1254, 1093, 1019, 835 cm^{-1}; ^1H NMR (400 MHz, D_2O) δ 7.14, 6.76 (AB q, 4 H, J = 8.4 Hz), 4.44 (d, 1 H, J = 8 Hz), 3.77 (d, 1 H, J = 1.2 Hz), 2.34 (m, 1 H), 0.70 (d, 3 H, J = 7.2 Hz); MS (FAB) 226 (M^+ + H), 207; exact mass (FAB) calcd for $C_{11}H_{16}NO_4$ (M^+ + H), 226.1079, found (M^+ + H), 226.1048.

***N*-[(*R*)-α-Methylbenzyl]-2-(hydroxyimino)butanamide (30).** To a stirred solution of 2-oxobutanoic acid (10.2 g) was added dropwise α,α-dichloromethyl methyl ether (9.1 mL) dropwise over 30 min. The reaction mixture was warmed up to 60 °C until the evolution of HCl ceased. The reaction mixture was cooled to 25 °C and diluted with dry CH_2Cl_2 (100 mL) and further cooled to −78 °C. A solution of (*R*)-(+)-α-methylbenzylamine (15.5 mL) and Et_3N (16.8 mL) in anhydrous CH_2Cl_2 (20 mL) was added over 30 min. The reaction mixture was warmed up to 25 °C and poured into H_2O (100 mL), and the organic layer was removed. The aqueous layer was washed with CH_2Cl_2 (2 × 50 mL), and the combined organic extracts were washed with HCl (2 M; 2 × 50 mL) and saturated aqueous $NaHCO_3$ (2 × 50 mL), dried ($MgSO_4$), and evaporated. The residue was dissolved in MeOH (80 mL) and hydroxylamine hydrochloride (10.4 g) followed by Et_3N (21 mL) was added, and the mixture was allowed to stir for 12 h. The solution was evaporated, taken up in CH_2Cl_2 (60 mL), washed with HCl (2 M; 2 × 100 mL) and saturated aqueous $NaHCO_3$ (2 × 100 mL), dried ($MgSO_4$), and evaporated to yield the oxime **30** (15.08 g, 68%) as a pale yellow oil: bp 150 °C (0.2 mmHg); $[\alpha]_D$ +2.41° (c 1.33 in $CHCl_3$); IR (neat) 3280, 3067, 2975, 2940, 2880, 1658, 1630, 1515, 1452, 1000, 766, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.28 (s, 5 H), 7.01 (d, 1 H, J = 7.6 Hz), 5.14 (m, 1 H), 2.59 (q, 2 H, J = 7.6 Hz), 1.46 (d, 3 H, J = 6.8 Hz), 1.06 (t, 3 H, J = 7.6 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.4, 156.2, 142.8, 128.5, 127.3, 126.0, 48.8, 21.9, 17.0, 10.5; MS (EI) m/e 220 ($M^{•+}$), 205, 203, 175, 132, 120, 107, 105, 77. Anal. Calcd for $C_{12}H_{16}N_2O_2$: C, 65.43; H, 7.32; N, 12.72. Found: C, 65.47; H, 7.20; N, 13.07.

(4*S*,5*S*)-5-(4-Methoxyphenyl)-4-methyl-*N*-[(*R*)-α-methylbenzyl]-3-isoxazolinecarboxamide (31). To a stirred solution of the (*R*)-oxime **30** (4.2 g) in anhydrous THF (45 mL) was added TMEDA (9.51 mL). The solution was cooled to −78 °C, and *n*-BuLi (1.6 M in hexanes; 39.4 mL) was added dropwise. The reaction mixture was warmed to 0 °C during 1.5 h and recooled to −78 °C, and 4-methoxybenzaldehyde (freshly distilled; 2.56 mL) in anhydrous THF (11 mL) was added. The reaction mixture was stirred at −78 °C for 1 h and quenched by the addition of HOAc (11.2 mL). The mixture was warmed to 25 °C, poured into H_2O (65 mL), and extracted with Et_2O (2 × 100 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (2 × 100 mL), dried ($MgSO_4$), and evaporated to yield a yellow oil. The residue was dissolved in dry CH_2Cl_2 (25 mL), trifluoroacetic acid (1.9 mL) added, and the mixture was allowed to stir for 12 h. The reaction mixture was poured into saturated aqueous $NaHCO_3$ (50 mL), the organic layer was removed, and the aqueous layer was extracted with CH_2Cl_2 (2 × 25 mL). The combined organic layers were dried ($MgSO_4$) and evaporated. Chromatography of the residue on silica (1:4 EtOAc/hexanes) afforded a 1:1 mixture (by 400-MHz ^1H NMR) of the diastereoisomeric amides **31** and **32** (4.85 g, 75%) as a white solid. Fractional crystallization from EtOAc/hexanes afforded the pure (4*S*,5*S*)-amide **31** (2.25 g, 35%) as a white crystalline solid: mp 122–123 °C (lit.[6] mp for enantiomer 123 °C); $[\alpha]_D$ +294° (c 1.01 in $CHCl_3$) [(lit.[6] rotation for enantiomer $[\alpha]_D$ −310° (c 0.845 in $CHCl_3$)]; IR (KBr) 2358, 2950, 1652, 1620, 1591, 1520, 1460, 1390, 1311, 1254, 1182, 1040, 940, 920, 852, 822, 706 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.35 (s, 5 H), 7.28 (br m, 1 H), 7.24, 6.90 (AB q, 4 H, J = 8.8 Hz), 5.18 (m, 2 H), 3.81 (s, 3 H), 3.57 (m, 1 H), 1.55 (d, 3 H, J = 6.9 Hz), 1.43 (d, 3 H, J = 6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.9, 158.7, 156.7, 142.6, 131.1, 128.8, 127.5, 127.3, 126.1, 114.2, 92.2, 55.3, 49.4, 49.0, 22.0, 17.1; MS (EI) m/e 338 ($M^{•+}$), 234, 217, 148, 120, 105; exact mass (EI) calcd for $C_{20}H_{22}N_2O_3$ ($M^{•+}$), 338.1632, found ($M^{•+}$), 338.1644.

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