remaining at this point was mixed with 30 mL of ethyl acetate, and the resulting suspension was extracted with three 25-mL portions of 1 N HCl and one 25-mL portion of brine. The dried ($MgSO_4$) organic layer was concentrated using a rotary evaporator, the material remaining was once again taken up in ethyl acetate, extracted thrice with 1 N HCl, dried, concentrated, and recrystallized (isopropyl alcohol) to give 1.33 g (2.36 mmol, 70%) of a white solid: IR (KBr) 3300, 1760, 1700, 1650, 1240 cm^{-1}; NMR (DMSO-d_6, 300 MGz) δ 2.77 (dd, J = 10.9, 13.8 Hz, 1 H), 3.06 (dd, J = 3.8, 13.8 Hz, 1 H), 3.78 (d, J = 5.9, 4 H), 4.30 (m, 1 H), 4.94 (s, 2 H), 5.26 (s, 2 H), 7.12–7.46 (m, 14 H), 7.58 (d, J = 8.5 Hz, 1 H), 8.14 (t, J = 5.9 Hz, 1 H), 8.37 (t, J = 5.7 Hz, 1 H), 12.59 (s, 1 H).

Anal. Calcd for $C_{29}H_{29}N_3O_9 \cdot 1.5H_2O$: C, 58.97; H, 5.47; N, 7.11. Found: C, 59.35; H, 5.29; N, 7.05.

This material, as a solution in 2 mL of DMF, was loaded onto 2.00 g of oxime resin using 0.281 g (1.36 mmol) of DCC in 20 mL of CH_2Cl_2, by a procedure analogous to that described for the Boc-Gly-Resin above.

***N*-Carbobenzyloxy-*O*-carbobenzyloxy-L-tyrosylglycyl-glycyl-L-phenylalanine 4-(Methylthio)phenyl Ester (3a).** A suspension of 1.00 g of the (N-Z,O-Z)-Tyr-Gly-Gly-Resin described above (ca. 0.50 mequiv) and 0.208 g of H-Phe-OMMP·HBr (0.56 mmol) in 9 mL of CH_2Cl_2 was stirred and treated with 35 μL of acetic acid (0.62 mmol) and 100 μL of DIEA. After 10 min, the reaction mixture was filtered through a medium-porosity sinter into 60 mL of CH_2Cl_2, and the resin mass was washed with 5-mL portions of DMF, methanol, and CH_2Cl_2. The combined filtrate was washed twice with 50-mL portions of 1 N HCl and once with a 50-mL portion of brine. The organic layer was dried (Na_2SO_4), filtered, and concentrated to yield 0.160 g (0.233 mmol, 44%) of a slightly yellow solid which could be recrystallized from isopropyl alcohol: NMR (DMSO-d_6, 300 MHz) δ 2.75 (dd, 1 H), 3.05 (dd, 1 H), 3.02 (m, 2 H), 3.33 (s, 3 H), 3.99 (d, 4 H), 4.28 (m, 1 H), 4.62 (m, 1 H), 4.94 (s, 2 H), 5.26 (s, 2 H), 6.87 (d, 2 H), 7.12 (d, 2 H), 7.18–7.48 (m, with d, 17 H), 7.42 (d, 2 H), 7.58 (d, 1 H), 8.11 (t, 1 H), 8.37 (t, 1 H), 8.56 (d, 1 H); the assumed structure of the product was consistent with the 2D-COSY spectrum of this material.

Anal. Calcd for $C_{45}H_{44}N_4O_{10}S$: C, 64.88; H, 5.34; N, 6.72. Found: C, 64.95; H, 5.42; N, 6.68.

***N*-Carbobenzyloxy-*O*-carbobenzyloxy-L-tyrosylglycyl-glycyl-L-phenylalanine 4-(Methylsulfonyl)phenyl Ester (3b).** A 45-mg (0.056-mmol) portion of **3a** was taken up in 1.0 mL of chloroform and mixed with ca. 1 mg of methyltricaprylammonium chloride. This material was mixed with a solution of 200 mg of 80% MMPP (0.32 mmol active reagent, 5.7-fold excess) in 2 mL of water, and the resulting two-phase system was stirred vigorously for 6 h. The organic layer was separated and extracted with three 2-mL portions of 5% $NaHCO_3$, two 2-mL portions of water, and one 2-mL portion of brine. After drying ($Na_2SO_4/MgSO_4$), the chloroform solution was concentrated using a rotary evaporator to give 41 mg (0.047 mmol, 85%) of a white solid. Recrystallization from ethyl acetate/hexane gave 18 mg of a crystalline material; NMR ($CDCl_3$, 300 MHz) δ 2.90 (s, 3 H), 2.86–3.04 (m, 2? H), 3.13 (dd, 2 H), 3.66–3.91 (m, 4 H), 4.30 (q, 1 H), 4.85–4.96 (m, 3 H), 5.14 (s, 2 H), 5.58 (d, 1 H), 6.96–7.07 (m, with d, J = 8.8 Hz, 6 H), 7.13–7.35 (m, 15? H), 7.78 (d, J = 8.7 Hz, 2 H), 7.99 (t, 1 H).

Anal. Calcd for $C_{45}H_{44}N_4O_{12}S$: C, 62.48; H, 5.14; N, 6.47. Found: C, 62.92; H, 5.33; N, 6.50.

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N-(9-Phenylfluoren-9-yl)-α-amino Ketones and *N*-(9-Phenylfluoren-9-yl)-α-amino Aldehydes as Chiral Educts for the Synthesis of Optically Pure 4-Alkyl-3-hydroxy-2-amino Acids. Synthesis of the C-9 Amino Acid MeBmt Present in Cyclosporin

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Serine-derived *N*-(9-phenylfluoren-9-yl)-α-amino ketones were prepared by acylation of primary organometallic reagents with amino acid isoxazolidides. When the amino and hydroxyl functions of serine were constrained in oxazolidine and oxazolidinone rings, alkylation of these ketones as their lithium enolates proceeded regiospecifically with good to excellent diastereoselectivity. Reduction of the oxazolidine and oxazolidinone ketones diastereoselectively led to N-protected 4-alkyl-branched 2-amino 1,3-diols that were subsequently oxidized in two steps, via the *N*-(9-phenylfluoren-9-yl)-α-amino aldehyde, to produce 4-alkyl-β-hydroxy-α-amino acids. In this way, L-(+)-MeBmt (1), the C-9 amino acid of cyclosporin, and its D-(−) enantiomer were prepared in 12 steps from D- and L-serine, respectively, with 22% overall yield and >99% enantiomeric purity. *N*-(9-Phenylfluoren-9-yl)-MeBmt triple-bond and 6*Z* double-bond analogues **37** and **39** were also prepared. This synthetic route requires only a single chiral source (serine) and provides for configurational choice and control at all four diastereomeric centers.

Introduction

(2*S*,3*R*,4*R*,6*E*)-3-Hydroxy-4-methyl-2-(methylamino)-6-octenoic acid (MeBmt (1)) is the unique C-9-amino acid constituent of the immunosuppressive drug cyclosporin.[1] Structurally, **1** is related to (2*S*,3*S*,4*S*)-3-hydroxy-4-methylproline (Hmp), which is found in the antifungal lipopeptide echinocandin D.[2] MeBmt may be classified among both β-hydroxy-α-amino acids[3] and γ-alkyl-

(1) MeBmt is the IUPAC/IUB three-letter notation for (4*R*)-4-((*E*)-2-butenyl)-4,*N*-dimethyl-L-threonine.

(2) (a) Kurokawa, N.; Ohfune, Y. *J. Am. Chem. Soc.* **1986**, *108*, 6041, 6043. (b) Evans, D. A.; Weber, A. E. *J. Am. Chem. Soc.* **1987**, *109*, 7151. (c) Mulzer, J.; Becker, R.; Brunner, E. *J. Am. Chem. Soc.* **1989**, *111*, 7500.

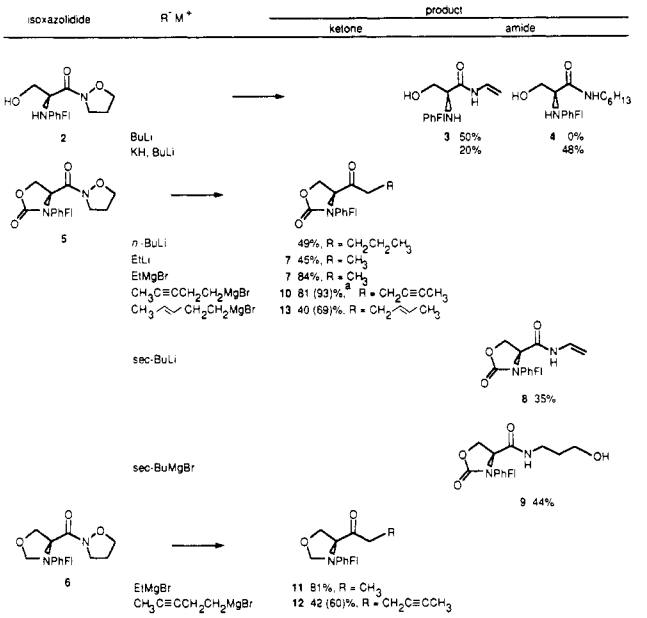
0022-3263/90/1955-3511$02.50/0

branched α-amino acids, both of which show interesting biological activity alone and as peptide constituents.[4] MeBmt shows no biological activity; however, modification of the MeBmt moiety in cyclosporin greatly affects the immunosuppressive activity of this important therapeutic agent.[5]

Cyclosporin is a neutral, hydrophobic, conformationally rigid, cyclic undecapeptide, isolated from the fungal species *Tolypocladium inflatium* Gams.[6] It prevents organ and bone marrow graft rejection after transplantation.[7,8] Exploration of cyclosporin's mechanism of action with analogues has demonstrated the importance of the MeBmt residue to the immunosuppressive activity of the peptide. Reactions on the MeBmt amino acid residue within the cyclosporin peptide have produced a series of analogues that exhibit decreased activity relative to the parent peptide.[7b,9] These reactions include catalytic hydrogenation to reduce the Δ^6 double bond, acylation of the secondary hydroxyl group, and oxidation of the double bond with ozone and *m*-chloroperbenzoic acid.

The other ten cyclosporin amino acids are commonly occurring natural amino acids, yet MeBmt must be prepared by total synthesis. Since MeBmt can be conveniently incorporated by the usual peptide synthesis methodology into cyclosporin, the current difficulty in preparing a wider variety of cyclosporin analogues results from deficient methodology to synthesize γ-alkyl-β-hydroxy-α-amino acids like MeBmt with configurational control. Synthesis of **1** was first achieved in 24 steps and 7.8% yield from (*R,R*)-(+)-tartaric acid.[10] Since then asymmetric epoxidation of a dienol has been used to prepare **1** of 94% enantiomeric excess through a route that merges with that of the original synthesis.[11] Also an asymmetric aldol condensation between a glycine enolate carrying a chiral auxiliary and (2*R*,4*E*)-2-methyl-4-butenal has allowed synthesis of enantiomerically pure **1** as well as its 4*S* alkyl-branched diastereomer.[12,13] Incorporation of the 4*S* diastereomer into cyclosporin produced a peptide with 2–4% of the immunosuppressive activity of cyclosporin.[14] A lengthy linear synthesis of **1** was avoided with the convergent glycine–aldol approach; however, the necessity for both the chiral auxiliary on the glycine enolate, which is needed to ensure diastereoselectivity, and the chiral α-alkyl-branched aldehyde, which is required for introduction of the γ-alkyl-branched stereocenter, makes the aldol approach limited for the versatile, large-scale preparation of MeBmt analogues.

Table I. Acylation of Organometallic Reagents with *N*-PhFl-Amino Acid Isoxazolidides



[a] Value in parentheses is based on consumed isoxazolidide. Enantiomerically pure isoxazolidide was recovered and recycled.

We now present a general method for synthesis of γ-alkyl-branched β-hydroxy-α-amino acids and have applied it for the preparation of **1** from serine in 22% overall yield and >99% enantiomeric purity. Our method is amenable to large-scale production of MeBmt analogues and is specifically designed to make variations at the γ-alkyl-branched center of **1** through regioselective enolization and alkylation of common *N*-(9-phenylfluoren-9-yl)(PhFl)-amino ketone intermediates prepared from L- and D-serine.[15] Both double-bond isomers at C-6,7 of MeBmt were also synthesized from a common triple-bond intermediate. Addition of nucleophiles to the ketone function of the alkylated products should allow for stereoselective introduction of other functionality at the β-position of MeBmt.[16] Finally, a two-step oxidation of the primary alcohol, passing through a configurationally stable α-amino aldehyde, provides **1** of >99% enantiomeric purity in either D-(−) or L-(+) stereochemistry, dependent only on the choice of chiral α-amino acid educt.

Results and Discussion

Acylation of Organometallic Reagents with *N*-PhFl-Serine Isoxazolidides. To achieve our objective, an efficient synthesis of *N*-PhFl-amino ketones from serine was needed. *N*-PhFl-Amino ketones were previously prepared from L-alanine via oxidation of amino alcohols obtained from acylation of organometallic reagents with the configurationally stable *N*-PhFl-amino aldehyde.[17] Direct addition of organometallic reagents to N-protected

(3) Previous syntheses of β-hydroxy-α-amino acids are reported in: Roemmele, R. C.; Rapoport, H. *J. Org. Chem.* **1989**, *54*, 1866 and references therein.

(4) Syntheses of γ-substituted prolines are reported in: Koskinen, A. M. P.; Rapoport, H. *J. Org. Chem.* **1989**, *54*, 1859 and references therein. Syntheses of other γ- and β-substituted α-amino acids are reviewed in: Wanger, I.; Musso, H. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 816.

(5) The impact of cyclosporin on transplantation is presented in: (a) DeBakey, M. R. *Compr. Therapy* **1984**, *10*, 7. (b) Morris, P. J. *J. Adv. Surg.* **1984**, *17*, 99.

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(9) Wenger, R. M. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 77.

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(11) (a) Tung, R. D.; Rich, D. H. *Tetrahedron Lett.* **1987**, *28*, 1139. (b) Synthesis of 3-methyl-des-4-methyl-MeBmt via an asymmetric epoxidation: Sun, C.-Q.; Rich, D. H. *Tetrahedron Lett.* **1988**, *29*, 5205. (c) Rao, A. V. R.; Dhar, T. G. M.; Chakraborty, T. K.; Gurjar, M. K. *Tetrahedron Lett.* **1988**, *29*, 2069.

(12) Evans, D. A.; Weber, A. E. *J. Am. Chem. Soc.* **1986**, *108*, 6757.

(13) (a) Schmidt, U.; Siegel, W. *Tetrahedron Lett.* **1987**, *28*, 2849. (b) Aebi, J. D.; Dhaon, M. K.; Rich, D. H. *J. Org. Chem.* **1987**, *52*, 2881. (c) Togni, A.; Pastor, S. D.; Rihs, G. *Helv. Chim. Acta* **1989**, *72*, 1471.

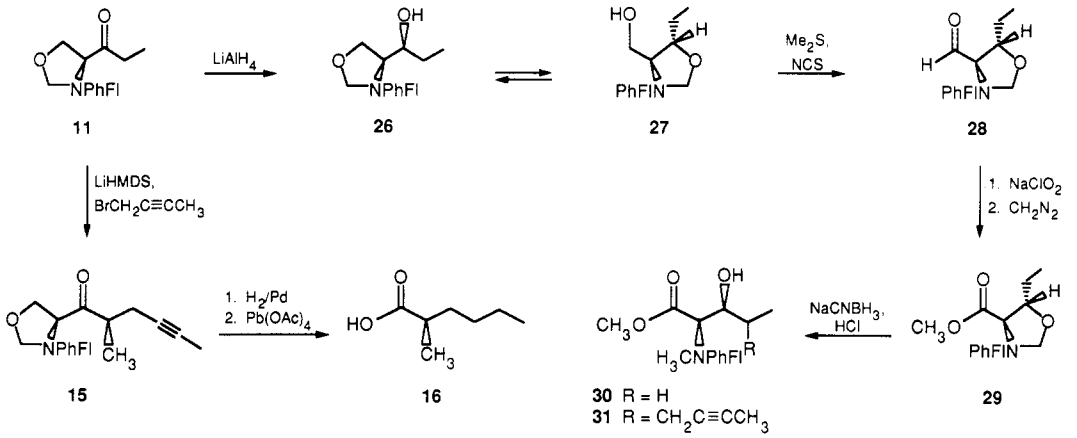
(14) Rich, D. H.; Sun, C.-Q.; Guillaume, D.; Dunlap, B.; Evans, D. A.; Weber, A. E. *J. Med. Chem.* **1989**, *32*, 1982.

(15) The synthesis of D-amino acids from L-serine is reported in: Maurer, P. J.; Takahata, H.; Rapoport, H. *J. Am. Chem. Soc.* **1984**, *106*, 1095.

(16) Maurer, P. J.; Knudsen, C. G.; Palkowitz, A. D.; Rapoport, H. *J. Org. Chem.* **1985**, *50*, 325.

(17) (a) Lubell, W. D.; Rapoport, H. *J. Am. Chem. Soc.* **1987**, *109*, 236. (b) Lubell, W. D.; Rapoport, H. *J. Am. Chem. Soc.* **1988**, *110*, 7447.

Scheme I. Selective Enolization, Alkylation, and Reduction of Oxazolidinone Ketones 7 and 10



α-amino acids furnishes α-amino ketones when the amine is protected as an amide,[18] sulfonamide,[15,19] or carbamate,[19] yet analogous acylation of primary organolithium or organomagnesium reagents using *N*-PhFl-amino acids was not successful. This gap was closed when we found that acylation of organometallic reagents with serine isoxazolides did provide an effective means to prepare *N*-PhFl-amino ketones.

In early attempts to prepare amino ketone by acylation of *n*-butyllithium with *N*-PhFl-serine isoxazolidide **2**, no amino ketone was isolated, and instead vinylamide **3** was formed from fragmentation of the isoxazolidide ring with loss of formaldehyde (Table I). Pretreating **2** with 250 mol % of potassium hydride in THF at room temperature in order to deprotonate the alcohol and amino groups, followed by cooling to −78 °C and adding *n*-butyllithium, again yielded no amino ketone. Instead *N*-hexylamide **4** was obtained as the major product in moderate (up to 50%) yield, along with vinylamide **3** and other products resulting from loss of the PhFl protecting group. Vinylamide **3** is postulated to arise from deprotonation of the methylene protons neighboring the isoxazolidine nitrogen, which in turn leads to elimination of formaldehyde. *N*-Hexylamide appears to be formed from *n*-butyl anion nucleophilically attacking the isoxazolidine central methylene carbon, causing fragmentation with displacement of formaldehyde.

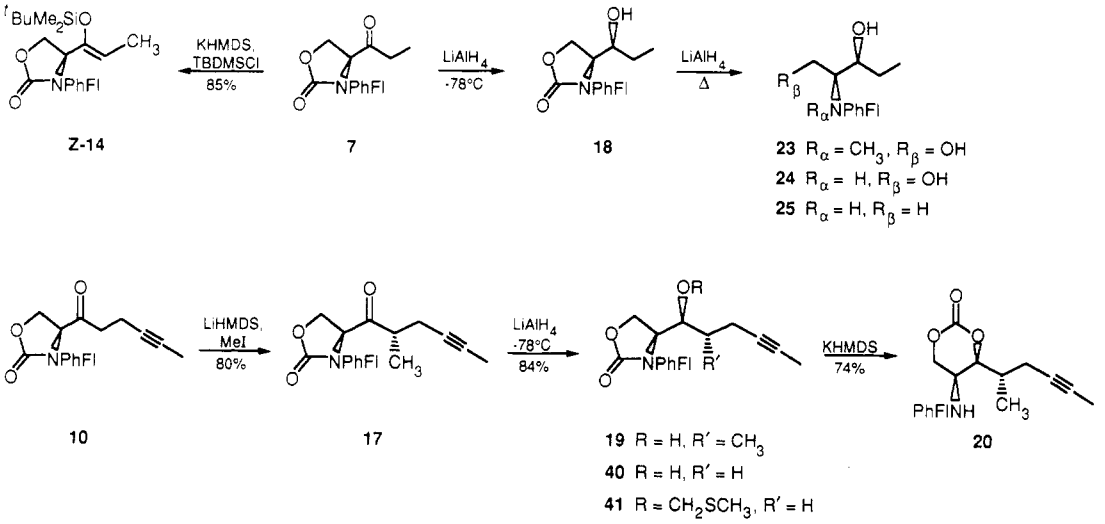
We next pursued protection of both the hydroxyl and amino functions of **2** by preparing the cyclic carbamate **5** with phosgene in toluene[20] and oxazolidine **6** with aqueous formaldehyde and catalytic toluenesulfonic acid in THF. Both oxazolidinone isoxazolidide **5** and oxazolidine isoxazolidide **6** readily acylated primary organolithium and Grignard reagents to produce amino ketones. Higher yields of amino ketone **7** were achieved in acylations with ethylmagnesium bromide than with ethyllithium, and the best yields were obtained with 400 mol % of Grignard reagent at 0 °C. Attempts to add *sec*-butyllithium to **5** also resulted in ring opening of the isoxazolidide with loss of formaldehyde to produce vinylamide **8**. Also attempts to acylate *sec*-butylmagnesium bromide with isoxazolidide **5** resulted in reductive cleavage of the isoxazolidide nitrogen–oxygen bond, producing the *N*-hydroxypropylamide **9**, instead of the desired γ-alkyl-α-amino β-ketone.

Although *N*-alkyl-*O*-alkylhydroxamates have been used to prevent overreduction during addition reactions to prepare aldehydes and ketones with little alcohol side products,[17a,20,21] fragmentation of the nitrogen–oxygen bond is a common problem when using these carboxylic acid derivatives. Loss of OCH_3 has been observed with both butyllithium and lithium diisopropylamide at −70 °C[22] and *N*-methyl-*O*-methylhydroxamates, leading to the formation of *N*-methylamide. Three different fragmentation patterns have been observed when using isoxazolidides. These include vinylamide formation, through proton abstraction and elimination of formaldehyde; *N*-hexylamide formation, through nucleophilic displacement of formaldehyde; and *N*-hydroxypropylamide formation, from reductive cleavage of the isoxazolidide ring. In our hands, preparation of *N*-PhFl-amino ketones without side products was best achieved through addition of primary Grignard reagents to oxazolidine and oxazolidinone *N*-PhFl-amino acid isoxazolidides.

Regioselective Enolization and Stereoselective Alkylations of *N*-PhFl-Amino Ketones. With both oxazolidinone and oxazolidine *N*-PhFl-amino ketones in hand, we began our investigation of enolization and alkylation conditions to control the alkyl branch stereochemistry as shown in Scheme I. Initially, enolization of oxazolidinone amino ketone **7** in the presence of strong sterically hindered bases was explored by trapping the enolate with *tert*-butyldimethylsilyl chloride (TBDMSCl). Previously, we showed that trapping the enolate of (2*S*)-*N*-(PhFl)-amino-3-heptanone, prepared with potassium hexamethyldisilazide (KHMDS) in THF, with TBDMSCl provided the (*Z*)-silyl enol ether.[17b] Treatment of **7** with KHMDS in THF followed by TBDMSCl also resulted in formation of a single silyl enol ether isomer **14**, which was assigned the *Z* configuration based on NOESY spectroscopy.[23] The (*Z*)-enolate appears to be the thermodynamic enol ether because it avoids steric interactions between the methyl group and the *N*-phenylfluorenyl-protected oxazolidinone ring. Attempts to prepare the (*E*)-silyl enol ether with lithium tetramethylpiperidide (LiTMP) in THF at −78 °C followed by trapping the enolate by silylation required the addition of 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU) to produce a 3.8/1 *E*/*Z* ratio of silyl enol ether **14**. Formation of the (*E*)-enolate of **7**

(18) Buckley, T. F., III; Rapoport, H. *J. Am. Chem. Soc.* **1981**, *103*, 6157.
(19) Knudsen, C. G.; Rapoport, H. *J. Org. Chem.* **1983**, *48*, 2260.
(20) Lubell, W. D.; Rapoport, H. *J. Org. Chem.* **1989**, *54*, 3824.
(21) (a) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815. (b) Cupps, T. L.; Boutin, R. H.; Rapoport, H. *J. Org. Chem.* **1985**, *50*, 3972. (c) Feherentz, J.-A.; Castro, B. *Synthesis* **1983**, 676.
(22) Personal communication from Dr. S. Graham, Merck, Sharp and Dohme, West Point, PA.
(23) Dipolar coupling was observed between the vinyl and oxazolidine ring protons, while no dipolar coupling was observed between the protons of the methyl group and any oxazolidine ring protons. Dipolar coupling was also observed between the methyl and TBDMS group protons.

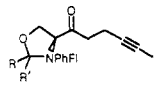
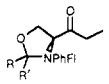
Scheme II. Conversion of Oxazolidine Ketone 11 to β-Hydroxy-α-methylamino Ester 30



with LiTMP may proceed through a tight transition state in which steric interactions between the side-chain methyl group and hindered base predominate over the interaction between the methyl and PhFl groups.[24] 1,3-Dimethylimidazolidinone (DMEU) and DMPU allow for silylation by breaking up the enolate complex; however, these urea additives may also allow the (*E*)-enolate to equilibrate to the thermodynamic (*Z*)-enolate before trapping with the silyl chloride.

Alkylation of lithium or potassium enolates of oxazolidinone and oxazolidine *N*-PhFl-amino ketones with alkyl halides in THF required a metal-coordinating cosolvent (DMPU, DMEU, HMPA, diglyme, or 18-crown-6-ether) for reaction at −78 °C.[25] When the potassium enolate of **7** was treated with methyl iodide, allyl bromide, or 1-bromo-2-butyne, products from both mono- and bisalkylation were obtained.[26] On the other hand, the lithium enolate of **7** reacted with alkyl halides to give predominantly monoalkylated products. Alkylation of oxazolidinone ketone enolates proceeded with higher stereoselectivity than oxazolidine ketone enolates (Table II). The stereochemistry of the alkylation products **15** and **17** was ascertained by treating γ-alkyl-branched diastereomeric mixtures of oxazolidine ketone **15** (Scheme II) with hydrogen and palladium on carbon in acetic acid in order to both saturate the triple bond and remove the phenylfluorenyl group; then oxidation of the secondary amino ketone acetate salts with lead tetraacetate produced α-methylhexanoic acid **16**, which was used for optical rotation comparisons with literature values.[17b,27] The proton NMR spectra of oxazolidine ketone **15** and oxazolidinone ketone **17** show that the γ-methyl group doublet is shifted downfield for the anti isomers relative to the syn isomers.

Table II. Alkylation of *N*-PhFl-Amino Ketones

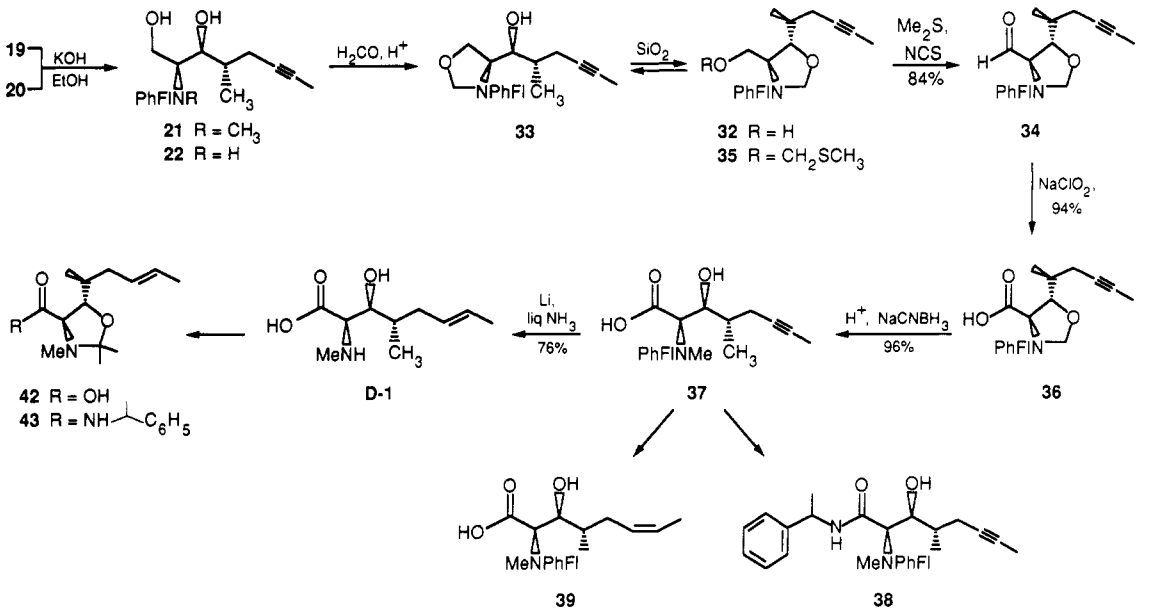
ketone	mol%, base	mol%, RX	vol% DMEU	time (h)	temp (°C)	anti/syn[a]	% yield[b]
							
10 R, R' = O	150, LiHMDS	125, CH_3I	10	2	0	20/1	80[c] (82)
12 R = R' = H	150, LiHMDS	110, CH_3I	5	1.5	0	1.5/1	54 (77)
							
7 R, R' = O	140, LiHMDS	140, $CH_3C{\equiv}CCH_2Br$	20[d]	5	-78	1/10	52 (77)
	140, LiTMP	140, $CH_3C{\equiv}CCH_2Br$	20[d]	5	-78	5/1	61 (78)
11 R = R' = H	150, LiHMDS	150, $CH_3C{\equiv}CCH_2Br$	20	3	0	1/3.5	71 (77)

[a] Anti/syn ratio was determined by ^1H NMR analyses of the crude reaction products. [b] Yield of isolated material; yield in parentheses is based on recovered amino ketone. [c] Yield of purified material of >96% diastereomeric excess. [d] DMPU was used in place of DMEU.

Synthesis of β-Hydroxy-*N*-methyl-α-amino Ester 30 and D-(−)-MeBmt. Completion of a synthesis of β-hydroxy-*N*-methyl-α-amino acids from oxazolidinone and oxazolidine *N*-PhFl-amino ketones requires reduction of the ketone, methylation of the nitrogen, and oxidation of the primary alcohol to a carboxylic acid. Oxazolidinone ketone **17** was obtained with the highest diastereomeric excess from alkylation of amino ketone **10** with methyl iodide. Thus, conversion of oxazolidinone ketones to *N*-methylamino acids was initially investigated. In our first attempt to reduce oxazolidinone ketones, a THF solution of lithium aluminum hydride was shown to stereoselectively reduce both **7** and **17** at −78 °C to produce amino alcohols **18** and **19** (Scheme I). In each case, the resulting β-hydroxyl group was set syn to the α-amino center. It has been reported that *N*-methyloxazolidinone alcohols can be equilibrated under basic conditions to form the more substituted oxazolidinone isomer;[11c] however, attempts to form the more substituted oxazolidinone isomer through migration of the carbamate of *N*-PhFl-oxazolidinone alcohol **19** with KHMDS at 0 °C resulted instead in formation of carbonate **20**. Similarly, attempts to alkylate the potassium alkoxide of **19** were thwarted by formation of carbonate **20**. Attempts to reduce the carbamate of oxazolidinone **19** to the *N*-methylamine with $LiAlH_4$ in refluxing THF gave *N*-methyl diol **21** in only 34% yield, accompanied by 34% of nor-methyl diol **22** from hydrolysis

(24) Corey, E. J.; Gross, A. W. *Tetrahedron Lett.* **1984**, *25*, 495.
(25) The effect of metal-coordinating solvents on enolate reactivity is reviewed in: Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1624. Hexamethylphosphoramide (HMPA) as solvent is reviewed in: Normant, H. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 1046.
(26) 1-Bromo-2-butyne and 1-bromo-3-pentyne were prepared through modification (see Experimental Section) of the procedure in: Hassan, M. A. *J. Chem. Soc. Pak.* **1983**, *5*, 103. Alkylation of the lithium enolate of oxazolidinone ketone **7** with 1-bromo-2-butyne gave 2% of the bis-alkylated product: ^1H NMR δ 0.62 (s, 3 H), 1.57 (dd, 1 H, J = 2.5, 16.8), 1.7 (t, 3 H, J = 2.2), 1.71 (t, 3 H, J = 2.2), 1.8 (dd, 1 H, J = 2.5, 16.8), 2.12 (dd, 1 H, J = 2.6, 6.3), 2.18 (dd, 1 H, J = 2.6, 6.2), 4.26 (dd, 1 H, J = 8.8, 3.9), 4.32 (t, 1 H, J = 9.3), 4.76 (dd, 1 H, J = 3.8, 9.4), 7.4–8.3 (m, 13 H).
(27) Klyne, W.; Buckingham, J. *Atlas of Stereochemistry. Absolute Configurations of Organic Molecules*; Oxford University Press: New York, 1974; p 65 and references therein.

Scheme III. Synthesis of D-MeBmt (D-1) from Amino Diol 22



of the carbamate. Also, exposure of oxazolidinone **18** to similar conditions resulted in N-methylated diol **23** (26%), along with nor-methyl diol **24** (24%) from hydrolysis, and amino alcohol **25** (28%) from reductive cleavage of the methylene carbon–oxygen bond (Scheme I)

Somewhat discouraged by early attempts to convert oxazolidinone ketones to β-hydroxy-*N*-methylamino acids, we examined the transformation of oxazolidine ketone **11** to *N*-methylamino ester **30** (Scheme II). We found that reduction of oxazolidine ketone **11** with $LiAlH_4$ was accompanied by Lewis acid mediated migration to give alcohol **27** as a single isomer in quantitative yield (Scheme II). Oxidation of **27** with *N*-chlorosuccinimide and dimethyl sulfide provided aldehyde **28** in 73% yield accompanied by 6% of amino ketone **11**, indicating that migration of the methylene group and oxidation of **26** occurred.[17b,20,28] Assignment of syn stereochemistry to the carbinol was based on the 7.4-Hz coupling constant between the α- and β-hydrogens of aldehyde **28**.[29] Sodium chlorite oxidation of aldehyde **28** followed by treatment of the acid with diazomethane produced methyl ester **29**.[30] Conversion of oxazolidine **29** to *N*-methyl alcohol **30** with $NaCNBH_3$ and HCl in THF afforded β-hydroxy-*N*-methylamino ester **30** in 90% yield.[31]

This success prompted us to investigate the conversion of oxazolidine ketone **15** to β-hydroxy-*N*-methylamino ester **31**. Although it was possible to prepare **31**, separation of the diastereomers of **15** was not possible by chromatography on silica gel and only a γ-alkyl diastereomeric mix of **31** was obtained. Ester **31** could, however, be recrystallized to yield diastereomerically enhanced mixtures. Rather than investigate other conditions to improve the diastereoselectivity in the alkylation of oxazolidine ketone, we sought instead to merge our highly stereoselective route to alkyl-branched oxazolidinone ketones with the oxazolidine approach to *N*-methylamino acids. On the basis of the observation that reduction of oxazolidine ketone **11** under Lewis acid conditions yielded more substituted oxazolidine alcohol **27**, we projected that treatment of *N*-PhFl-amino diol **22** with formaldehyde and acid would provide more substituted oxazolidine **32** instead of **33**.

Diol **22** was prepared by hydrolysis of carbamate **19** or carbonate **20** with refluxing ethanolic potassium hydroxide (Scheme III). Treatment of diol **22** with excess aqueous formaldehyde and catalytic toluenesulfonic acid in THF for 24 h followed by a bicarbonate quench and chromatography on silica gel (270–400 mesh) produced the desired oxazolidine **32** as the only product in 90% yield. Chromatography of the crude reaction mixture on less active (70–270 mesh) silica gel did allow isolation of less substituted oxazolidine isomer **33**. Isomer **33** could be equilibrated to **32** on exposure to the higher mesh silica gel.

Oxidation of the primary alcohol of **32** with *N*-chlorosuccinimide and dimethyl sulfide in toluene provided crystalline oxazolidine aldehyde **34** in 80% yield after chromatography, along with <5% of the (methylthio)-methyl ether **35**.[20,32] The proton NMR spectrum of aldehyde **34** showed a 6.7-Hz coupling constant between the C-4 and C-5 trans protons of the oxazolidine and confirmed the syn stereochemistry about the amino and alcohol functions.[29] Oxidation of aldehyde **34** with sodium chlorite rapidly produced carboxylic acid **36**, which was obtained in 94% yield after isolation and crystallization from ethyl acetate and hexane.[30] Previously, reduction of oxazolidine esters with $NaCNBH_3$ and acid in THF produced *N*-methylamino esters in high yield after chromatography, yet esterification and subsequent cleavage of the ester prior to the dissolving-metal reduction of the triple bond require two additional synthetic steps that are avoided by direct reduction of oxazolidine acid **36** with $NaCNBH_3$ to prepare *N*-methylamino acid **37**. Reduction of oxazolidine **36** was best accomplished with 800 mol % of $NaCNBH_3$ and 300 mol% of trifluoroacetic acid in THF at 0 °C to provide the *N*-PhFl-MeBmt triple-bond analogue **37** in 96% yield.

Enantiomeric purity of *N*-PhFl-MeBmt triple-bond analogue **37** was determined with both D- and L-**37** by

(28) Corey, E. J.; Kim, C. U. *J. Am. Chem. Soc.* **1972**, *94*, 7586.

(29) No direct comparison of coupling constant data for *N*-alkyloxazolidines is available; however, the data are consistent with those for *N*-Boc-oxazolidines (Garner, P.; Park, J. M. *J. Org. Chem.* **1987**, *52*, 2361) as well as for 2-oxazolidinones and 2-phenyl-2-oxazolines (Futagawa, S.; Inui, T.; Shiba, T. *Bull. Chem. Soc. Jpn.* **1973**, *46*, 3308).

(30) Bal, B. S.; Childers, W. E., Jr.; Pinnick, H. W. *Tetrahedron* **1981**, *37*, 2091.

(31) Lane, C. F. *Synthesis* **1975**, 135.

(32) (a) Johnson, C. R.; Phillips, W. G. *J. Am. Chem. Soc.* **1969**, *91*, 682. (b) Omura, K.; Sharma, A. K.; Swern, D. *J. Org. Chem.* **1976**, *41*, 957.

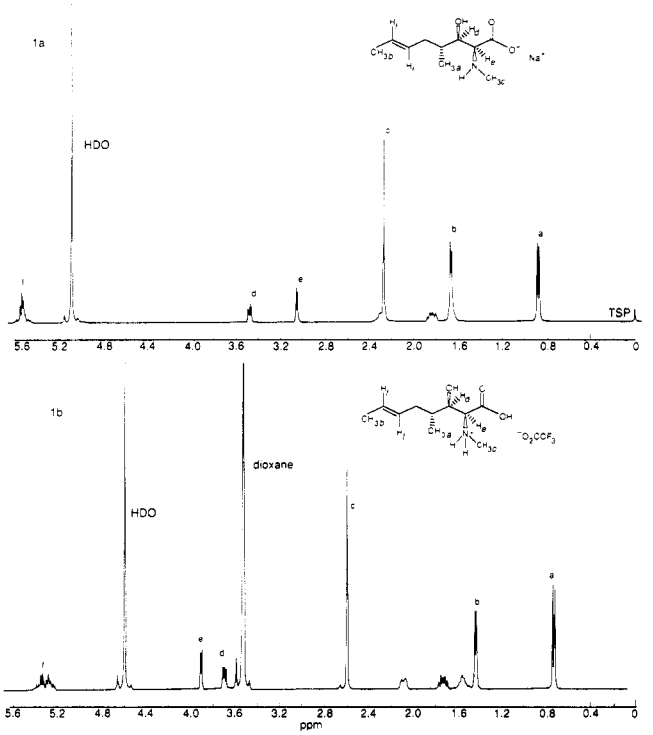


Figure 1. (a) ^1H NMR spectrum of MeBmt in D_2O/NaOD with deuterio-γ-(trimethylsilyl)propanoic acid as internal standard. (b) ^1H NMR spectrum of MeBmt in D_2O/trifluoroacetic acid with dioxane as internal standard.

coupling to (*R*)-α-methylbenzylamine with dicyclohexylcarbodiimide and hydroxybenzotriazole to produce amides **38**, which were assayed for diastereomeric purity by analysis of their proton NMR spectra. Examination of the *N*-methyl ^1H NMR singlets of amides **38** using incremental doping experiments established triple-bond analogue **37** to be of >99% enantiomeric purity.[33]

Reduction of triple-bond analogue **37** with Lindlar's catalyst provided the *N*-PhFl-MeBmt cis-double-bond isomer **39** with no loss of the phenylfluorenyl group.[34] In previous work directed to the synthesis of sphingosine from α-amino ynones, lithium in liquid ammonia was used to simultaneously remove a carbobenzyloxy amino protecting group and reduce a triple bond stereoselectively to a trans double bond.[35] Using this precedent, we subjected *N*-PhFl-amino acid **37** to lithium in liquid ammonia and obtained D-(−)-MeBmt in 79% yield as a hygroscopic solid after purification of the ammonium salt on cation-exchange resin. Purification of the lithium/liquid ammonia reduction product on anion-exchange resin provided MeBmt samples that were less hygroscopic in 76% yield.

In comparing our proton NMR data for **1** with literature values, we were surprised to find that the published NMR data for synthetic MeBmt, while claimed as coincident, all have different sets of chemical shift and coupling constant data.[10,12,13b] These differences may result from concentration effects as well as from the pH at which the NMR data were recorded. To avoid any ambiguities, we obtained an authentic (natural) sample of **1** and established a protocol for measuring the ^1H NMR spectrum of **1** in deuterium oxide as the sodium salt (Figure 1a) or trifluoroacetic acid salt (Figure 1b) with deuterio-γ-(trimethylsilyl)propanoic acid (TSP) or dioxane as internal standards. These spectra illustrate the effect of pH on the NMR coupling constants and chemical shifts for MeBmt. In particular, the state of ionization has a pronounced influence on the chemical shifts of the α- and β-protons. In alkaline solution (pH ~11), the β-proton is downfield relative to the α-proton. In acid (pH ~1), the positions are reversed. With these defined and controlled conditions, the sample of **1** we have synthesized was shown to be identical with the authentic sample.[36]

Synthesis of L-(+)-MeBmt. The naturally occurring enantiomer, L-(+)-MeBmt, was prepared from D-serine with a slight modification of the synthesis for D-(−)-MeBmt. The chromatographic separation of diastereomers **17** from alkylation of amino ketone **10** was avoided, and the crude alkylation product instead was reduced directly with $LiAlH_4$ to amino alcohol diastereomer **19** which was obtained from **10** in 73% yield and >98% diastereomeric purity after medium-pressure liquid chromatography and recrystallization. Amino alcohol **40** (Scheme I) from reduction of unalkylated **10** was also produced in 13% yield from this process and recycled back into the synthesis by reoxidation with *N*-chlorosuccinimide and dimethyl sulfide to obtain **10** in 83% yield along with 2% of the (methylthio)methyl ether **41**.

Isomerically pure MeBmt was produced after the lithium/liquid ammonia reduction, indicating that no epimerization of the α-amino center occurred under these alkaline conditions. To ascertain the limits for detection of another isomer, we prepared diastereomeric amides **43** utilizing the procedure for peptide synthesis with **1**.[6] Thus **1** in refluxing acetone provided 2,2-dimethyloxazolidine **42**, which was coupled to (*R*)-(+)- and (*S*)-(−)-α-methylbenzylamine, mediated by dicyclohexylcarbodiimide and hydroxybenzotriazole in THF, to produce diastereomeric amides **43**. Observation in the proton NMR spectra of both the γ-methyl group doublets and the α-proton doublets of **43** using incremental doping experiments demonstrated that amide **43** was of >99% diastereomeric purity and that no epimerization at the α-center occurred.

Conclusion

Regioselective alkylation and reduction of *N*-(9-phenylfluoren-9-yl)serine-derived oxazolidine and oxazolidinone ketones stereoselectively provides γ-alkyl-β-hydroxy-α-amino diols that are oxidized to yield γ-alkyl-β-hydroxy-α-amino acids. To demonstrate the efficiency of this method, (2*S*,3*R*,4*R*,6*E*)-3-hydroxy-4-methyl-2-(methylamino)-6-octenoic acid (**1**), the C-9 amino acid of the immunosuppressant drug cyclosporin, was prepared in 12 steps from serine with 22% overall yield and >99% enantiomeric purity. New triple-bond and cis-double-bond

(33) Proton NMR analysis was done according to: Maple, S. R.; Allerhand, A. *J. Am. Chem. Soc.* **1987**, *109*, 6609. Coupling of both D- and L-**37** to α-methylbenzylamine with dicyclohexylcarbodiimide produced amides **38** contaminated with *N*-acylurea side products. When excess hydroxybenzotriazole was added to intercept the *O*-acylisourea intermediate, amides **38** were obtained in 44% yield. We also found that diastereomerically pure amide **38**, contaminated with a less polar side product, could be produced when BOPCl was used as the coupling reagent as described in: Diago-Meseguer, J.; Palomo-Coll, A. L.; Fernandez-Lizarbe, J. R.; Zugaza-Bilbao, A. *Synthesis* **1980**, 547.

(34) Lindlar's catalyst was obtained from Alpha Chemicals. 6*Z*-MeBmt-Cyclosporin was previously prepared by acylation of the β-hydroxyl group of the MeBmt residue, oxidation of the 6,7-olefin to an aldehyde, and coupling in a Wittig reaction. It exhibits immunosuppressive activity equipotent to that of cyclosporin. (a) Park, S. B.; Meier, G. P. *Tetrahedron Lett.* **1989**, *30*, 4215. (b) European Patent 296122, 1988.

(35) Boutin, R. H.; Rapoport, H. *J. Org. Chem.* 1986, *51*, 5320. For deprotection of sulfonamides with dissolving-metal reductions, see: Roemmele, R. C.; Rapoport, H. *J. Org. Chem.* **1988**, *53*, 2367.

(36) We thank Dr. R. M. Wenger, Sandoz Ltd., Basel, Switzerland, for generously providing us with an authentic sample of MeBmt that was obtained from natural sources and shown to possess physical properties identical with those of material synthesized in ref 10.

MeBmt analogues were also prepared in N-protected form and used in amide coupling reactions. Considering the availability of both enantiomers of serine as well as the wide range of electrophiles that add to ketone enolates, this method provides a most versatile means for preparing these unique amino acids in optically pure form. This synthetic route requires only a single chiral source and provides for configurational choice and control at all four diastereomeric centers.

Experimental Section

General. Unless otherwise noted all reactions were conducted under a nitrogen or argon atmosphere, and distilled solvents were transferred by syringe. Tetrahydrofuran (THF) was distilled from $LiAlH_4$, 2-methyl-2-butene from sodium, and diethyl ether from sodium/benzophenone immediately before use; dimethylformamide (DMF), hexamethylphosphoramide (HMPA), ethanol, hexamethyldisilazane, 2,2,6,6-tetramethylpiperidine, toluene, 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU), and 1,3-dimethylimidazolidinone (DMEU) were distilled from CaH_2. Final reaction mixture solutions were dried over Na_2SO_4 before filtration and evaporation. Chromatography was on 230–400-mesh silica gel, and TLC was on aluminum-backed silica plates. Melting points were determined on a Swissco melting point apparatus and are uncorrected. ^1H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$. Chemical shifts are reported in ppm (δ units) downfield of internal tetramethylsilane ($(CH_3)_4Si$), and coupling constants are given in hertz.

L-*N*-(9-Phenylfluoren-9-yl)serine *N'*-Vinylamide (3) and L-*N*-(9-Phenylfluoren-9-yl)serine *N'*-Hexylamide (4). To a suspension of prewashed KH (280 mg, 7 mmol) in 5 mL of THF at 0 °C was added isoxazolidide **2** (1.2 g, 3 mmol) in THF (25 mL). After the mixture was stirred for 10 min, it was allowed to reach room temperature, stirred for 50 min, cooled to −78 °C, and treated with a solution of *n*-butyllithium in hexane (3 mL, 4.5 mmol) added over 1 h by syringe pump. After stirring for 2.5 h at −78 °C, the solution was treated with excess MeOH (1 mL), poured into 1 M KH_2PO_4 (25 mL), and extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine (50 mL), dried, and evaporated to an oil which was chromatographed on silica gel (100 g) with a gradient of 25–75% EtOAc in hexane as eluant. Vinylamide **3** (240 mg, 20%) eluted first: ^1H NMR δ 2.51 (t, 1 H, J = 4.6), 3.15 (dd, 1 H, J = 4.3, 10.6), 3.6 (dd, 1 H, J = 4.3, 10.9), 4.43 (d, 1 H, J = 8.6), 4.69 (d, 1 H, J = 15.8), 6.7 (ddd, 1 H, J = 8.6, 9.2, 15.8), 7.2–7.4 (m, 11 H), 7.66 (m, 2 H), 8.98 (d, 1 H, J = 9.2); ^{13}C NMR δ 171, 149.2, 147.7, 143.7, 140.8, 140.2, 128.8, 128.77, 128.5, 128.2, 127.9, 127.85, 127.5, 125.8, 125.4, 124.7, 120.2, 120.1, 96.2, 72.7, 63.2, 58; IR ($CDCl_3$) 3360, 2960, 1690, 1650 cm^{-1}. Anal. Calcd for $C_{24}H_{22}N_2O_2$: C, 77.8; H, 6.0; N, 7.6. Found: C, 77.5; H, 6.2; N, 7.5. Hexylamide **4** (550 mg, 48%, as a glass) eluted next: ^1H NMR δ 0.79 (t, 3 H, J = 6.8), 1.14 (m, 4 H), 1.35 (m, 1 H), 1.58 (m, 3 H), 2.47 (t, 1 H, J = 6.5), 3.1–3.5 (m, 4 H), 7.1–7.4 (m, 11 H), 7.63 (m, 2 H); ^{13}C NMR δ 176.5, 149, 147.9, 144.2, 140.9, 140.1, 128.5, 128.47, 128.3, 127.9, 127.4, 127.3, 125.9, 125.88, 124.6, 120, 119.9, 72.9, 58.8, 56.6, 35.5, 34.5, 32.1, 27.2, 22.3, 13.8. Anal. Calcd for $C_{28}H_{32}N_2O_2$: C, 78.5; H, 7.5; N, 6.5. Found: C, 78.8; H, 7.4; N, 6.9.

(4*S*)-3-(9-Phenylfluoren-9-yl)oxazolidine-4-carboxylic Acid Isoxazolidide (6). Isoxazolidide **2** (10 g, 25 mmol), formaldehyde (37 wt % solution in H_2O, 28 mL, 0.375 mol), and *p*-toluenesulfonic acid monohydrate (300 mg, 1.5 mmol) were dissolved in 200 mL of THF and stirred for 24 h at room temperature. The solution was washed with 50 mL of saturated sodium bicarbonate and 50 mL of brine, dried, and evaporated to a white solid which was heated at 70 °C under vacuum for 20 h to give **6** (10.1 g, 98%): mp 217 °C $[\alpha]^{20}_D$ −464° (*c* 2.6, $CHCl_3$); NMR δ 1.97 (m, 1 H), 2.04 (m, 1 H), 2.8 (m, 1 H), 3.3 (m, 1 H), 3.50 (m, 1 H), 3.60 (m, 1 H), 3.80 (m, 3 H), 4.77 (d, 1 H, J = 6.5), 4.93 (d, 1 H, J = 6.5), 7.1–7.8 (m, 13 H). Anal. Calcd for $C_{26}H_{24}N_2O_3$: C, 75.7; H, 5.9; N, 6.8. Found: C, 75.6; H, 6.0; N, 6.8.

General Procedure for Addition of Alkyllithium Reagents to Oxazolidinone Isoxazolidide 5. The alkyllithium reagent (1.5 mmol) in an inert solvent was added over 10 min to a −78 °C solution of **5** (1 mmol) in 10 mL of THF. The mixture was stirred for 0.25–1.5 h, poured into rapidly stirring 1 M KH_2PO_4 (10 mL), and extracted with EtOAc (3 × 10 mL). The organic layer was washed with brine, dried, and evaporated, and the residue was chromatographed with 50–100% EtOAc in hexane as eluant.

(4*S*)-2-Oxo-3-(9-phenylfluoren-9-yl)-4-(1'-oxopentyl)oxazolidine. *n*-Butyllithium was used as a 1.5 M solution in hexane to yield the amino ketone (49%): ^1H NMR δ 0.77 (t, 3 H, J = 7), 1.17 (m, 4 H), 1.5 (m, 1 H), 1.75 (m, 1 H), 3.87 (dd, 1 H, J = 4.1, 8.6), 4.08 (dd, 1 H, J = 4.1, 9.6), 4.3 (t, 1 H, J = 9.2), 7.15–7.8 (m, 13 H); ^{13}C NMR δ 207, 157.8, 146.5, 146.2, 140.2, 140.1, 139.9, 129.6, 129.3, 128.7, 128.5, 128.46, 128.2, 127.5, 126.7, 125.5, 120.1, 119.8, 72.7, 64.3, 62.6, 39.1, 24.6, 21.9, 13.7. Anal. Calcd for $C_{27}H_{25}NO_3$: C, 78.8; H, 6.1; N, 3.4. Found: C, 78.7; H, 6.2; N, 3.4.

(4*S*)-2-Oxo-3-(9-phenylfluoren-9-yl)-4-(1'-oxopropyl)oxazolidine (7). Ethyllithium was used as a 1 M solution in ether to yield **7** (45%): ^1H NMR δ 0.71 (t, 3 H, J = 7.1), 1.35 (m, 1 H), 1.79 (m, 1 H), 3.82 (dd, 1 H, J = 4.2, 8.5), 4.08 (dd, 1 H, J = 4.2, 9.6), 4.22 (t, 1 H, J = 9), 7.15–7.8 (m, 13 H); ^{13}C NMR δ 207.6, 157.8, 146.3, 146.2, 140.2, 140, 139.8, 129.6, 129.3, 128.7, 128.4, 128.37, 128.1, 127.4, 126.7, 125.5, 120, 119.8, 72.7, 64.3, 62.2, 32.9, 6.9. Anal. Calcd for $C_{25}H_{21}NO_3$: C, 78.3; H, 5.5; N, 3.7. Found: C, 78.4; H, 5.7; N, 4.0.

(4*S*)-2-Oxo-3-(9-phenylfluoren-9-yl)oxazolidine-4-carboxylic Acid Vinylamide (8). *sec*-Butyllithium was used as a 1 M solution in cyclohexane to yield **8** (35%, after recrystallization from CH_2Cl_2/hexane): mp 223–224 °C; $[\alpha]^{20}_D$ −464° (*c* 1.0, $CHCl_3$); ^1H NMR δ 3.9 (d, 1 H, J = 15.6), 4.26 (m, 2 H), 4.4 (dd, 1 H, J = 3.7, 9.3), 4.59 (t, 1 H, J = 9), 6.46 (m, 1 H), 6.63 (br d, 1 H, J = 11.2), 7.2–7.78 (m, 12 H), 8.15 (d, 1 H); ^{13}C NMR δ 166.9, 157.5, 146.8, 144.6, 140.4, 140.2, 139.8, 130.1, 129.8, 129.1, 128.7, 128.5, 128.1, 127.7, 126.9, 126.7, 125, 120.5, 120.4, 97.9, 72.5, 66.2, 60.2. Anal. Calcd for $C_{25}H_{20}N_2O_3$: C, 75.7; H, 5.1; N, 7.1. Found: C, 75.4; H, 5.3; N, 7.2.

(4*S*)-2-Oxo-3-(9-phenylfluoren-9-yl)-4-(1'-oxopropyl)oxazolidine (7) and (4*S*)-3-(9-Phenylfluoren-9-yl)-4-(1'-oxopropyl)oxazolidine (11). To magnesium metal (1.64 g, 67.5 mmol) was added dropwise a solution of bromoethane (4.48 mL, 60 mmol) in 60 mL of diethyl ether over 20 min. After the addition was complete, the mixture was stirred for 1 h and then transferred via Teflon tubing into a solution of isoxazolidide (**5** or **6**, 15 mmol) in 150 mL of THF at 0 °C. The solution was stirred for 1 h at 0 °C, transferred via Teflon tubing into 200 mL of 1 M NaH_2PO_4, and extracted with EtOAc (3 × 100 mL). The combined organic layer was washed with brine, dried, and evaporated to a foam, which on recrystallization from CH_2Cl_2/hexanes gave oxazolidinone ketone **7** in 84% yield: mp 245–245.5 °C; $[\alpha]^{20}_D$ +25° (*c* 0.7, $CHCl_3$). Chromatography on silica gel (70 g) with 10% EtOAc in hexanes as eluant gave oxazolidine ketone **11** in 81% yield: mp 127–128 °C; $[\alpha]^{20}_D$ +328° (*c* 2, $CHCl_3$); ^1H NMR δ 0.95 (t, 3 H, J = 7.3), 2.51 (m, 2 H), 3.17 (dd, 1 H, J = 4.5, 7.9), 3.29 (t, 1 H, J = 7.8), 3.64 (dd, 1 H, J = 4.5, 7.9), 4.66 (d, 1 H, J = 6.7), 5.06 (d, 1 H, J = 6.7), 7.2–7.8 (m, 13 H); ^{13}C NMR δ 212, 148.8, 146.3, 143.6, 141.5, 139.2, 129, 128.6, 128.58, 128, 127.9, 127.5, 127, 126.8, 125.7, 119.9, 119.6, 85, 77.2, 67.6, 66.5, 32.6, 7.4. Anal. Calcd for $C_{25}H_{23}NO_2$: C, 81.3; H, 6.3; N, 3.8. Found: C, 81.3; H, 6.3; N, 3.7.

(4*S*)-2-Oxo-3-(9-phenylfluoren-9-yl)oxazolidine-4-carboxylic Acid (3'-Hydroxypropyl)amide (9). To isoxazolidide **5** (210 mg, 0.5 mmol) in THF (5 mL) at 0 °C was added 3 mL of *sec*-butylmagnesium bromide in THF (1.33 M). The solution was stirred for 1 h, quenched with MeOH (1 mL), and partitioned between NaH_2PO_4 (1 M, 10 mL) and EtOAc (10 mL). The aqueous layer was extracted with EtOAc (3 × 10 mL), and the combined organic layer was washed with brine, dried, and evaporated to a solid that was purified on a 2000-μm silica gel plate to yield 92 mg (44%) of **9**: ^1H NMR δ 1.25 (m, 1 H), 1.33 (m, 1 H), 2.85 (m, 2 H), 3.22 (m, 1 H), 3.35 (m, 1 H), 4.22 (dd, 1 H, J = 3.5, 8.9), 4.35 (dd, 1 H, J = 3.4, 9.3), 4.58 (t, 1 H, J = 9.1), 5.57 (br m, 1 H), 7.2–8.1 (m, 13 H).

1-Bromo-3-pentyne. To a suspension of bromotriphenylphosphonium bromide[37] (132.2 g, 313 mmol) in 1,2,4-trichloro-

(37) Vogel, A. *Vogel's Textbook of Practical Organic Chemistry*, 4th ed.; Langman Scientific and Technical: England, 1978; p 637–8.

benzene (650 mL) was added 3-pentyn-1-ol (20 mL, 216 mmol, 100 mol %) in dichloromethane (100 mL) over 2 h. The mixture was stirred at room temperature 18 h, diluted with hexane (200 mL), and filtered. The white cake was washed with hexane (150 mL), and the combined filtrate was distilled through a 20-cm Vigreux column under aspirator vacuum to give 23 g (72%) of bromide: ^{1}H NMR δ 1.79 (t, 3 H, J = 2.5), 2.70 (m, 2 H), 3.41 (t, 2 H, J = 7.3); bp 64–67 °C/40 mmHg (lit.[26] bp 64–65 °C/40 mmHg).

(4*S*)-2-Oxo-3-(9-phenylfluoren-9-yl)-4-(1′-oxo-4′-hexynyl)oxazolidine (10). To 3.6 g (150 mmol) of magnesium powder (Aldrich, 50 mesh) covered with 200 mL of THF was added 10 mL of a solution of 15 g of 1-bromo-3-pentyne (100 mmol) in 40 mL of THF. The suspension was heated to a gentle reflux and then cooled to 0–5 °C in an ice bath, and the remaining alkyl halide solution was added to the mixture over 45 min by syringe pump. After the addition was complete, the mixture was stirred at 0–5 °C for 3.25 h and then added via stainless steel cannula over 15 min to a −78 °C solution of isoxazolidide **5** (10 g, 23.5 mmol) in 300 mL of THF. This solution was warmed to 0 °C, stirred for 2 h, and then transferred via Teflon tubing into 200 mL of 1 M NaH_2PO_4. The aqueous layer was extracted with 25% isopropyl alcohol in $CHCl_3$ (3 × 100 mL), and the combined organic extracts were washed with brine, dried, and evaporated to a residue which was chromatographed with a gradient of 25–100% EtOAc in hexane as eluant. Ketone **10** (8 g, 81%) was eluted first as a foam (>99% pure by ^{1}H NMR analysis); recrystallization from EtOAc/hexane gave 7.8 g of white crystals: mp 159–160 °C; $[\alpha]^{20}_D$ −34° (c 1.4, $CHCl_3$); ^{1}H NMR δ 1.6 (m, 1 H), 1.68 (t, 3 H, J = 2.4), 2.1 (m, 3 H), 3.9 (dd, 1 H, J = 4.1, 8.8), 4.08 (dd, 1 H, J = 4.6, 9.6), 4.2 (t, 1 H, J = 9.3), 7.06–7.7 (m, 13 H); ^{13}C NMR δ 205.4, 157.7, 146.3, 146.1, 140.2, 139.9, 139.8, 129.6, 129.4, 128.7, 128.4, 128.3, 128.2, 127.5, 126.7, 125.5, 120.1, 119.9, 76.9, 76.4, 72.7, 63.8, 62.3, 38.9, 12.8, 3.3. Anal. Calcd for $C_{28}H_{23}NO_3$: C, 79.8; H, 5.5; N, 3.3. Found: C, 79.9; H, 5.7; N, 3.4. Isoxazolidide **5** (1.3 g, 13%) was eluted next. (4*R*)-**10** was obtained as a foam in identical yield: $[\alpha]^{20}_D$ +53° (c 0.5, $CHCl_3$).

(4*S*)-3-(9-Phenylfluoren-9-yl)-4-(1′-oxo-4′-hexynyl)oxazolidine (12). 1-Bromo-3-pentyne (1.18 g, 8 mmol) in 8 mL of diethyl ether was added dropwise to magnesium turnings (220 mg, 9 mmol) at a rate sufficient to maintain a gentle reflux, and the mixture was then stirred for 45 min at room temperature and 15 min at reflux. The organometallic reagent solution was transferred via Teflon tubing into a solution of isoxazolidide **6** (824 mg, 2 mmol) in 20 mL of THF at 0 °C, and the solution was stirred for 1 h at 0 °C and 45 min at room temperature and then transferred via Teflon tubing into 15 mL of 1 M NaH_2PO_4. The aqueous phase was extracted with ethyl acetate (3 × 10 mL), and the combined organic layer was washed with brine, dried, and evaporated to an oil which was chromatographed on silica gel with 5–100% EtOAc in hexanes as eluant to give **12** (340 mg, 42%): $[\alpha]^{20}_D$ +152° (c 0.7, $CHCl_3$); ^{1}H NMR δ 1.76 (t, 3 H, J = 2.5), 2.26 (m, 2 H), 2.75 (t, 2 H, J = 7.2), 3.16 (dd, 1 H, J = 4.4, 8), 3.29 (t, 1 H, J = 8.0), 3.64 (dd, 1 H, J = 4.4, 7.9), 4.65 (d, 1 H, J = 6.7), 5.04 (d, 1 H, J = 6.7), 7.2–7.8 (m, 13 H). Anal. Calcd for $C_{28}H_{25}NO_2$: C, 82.5; H, 6.2; N, 3.4. Found: C, 82.5; H, 6.5; N, 3.21. Isoxazolidide **6** (250 mg, 30%) was also recovered.

(*E*)-3-Penten-1-ol.[38] To a slurry of $LiAlH_4$ (5.33 g, 140 mmol) in triglyme (42 mL) and THF (8 mL) was added 3-pentyn-1-ol (5.0 mL, 54 mmol), while the temperature of the reaction mixture was maintained at 25 °C with cooling. The mixture was heated at reflux for 50 h, cooled to room temperature, poured onto 100 g of ice, acidified with 300 mL of 1 M HCl to pH 2, and extracted with ether (3 × 100 mL). The combined organic layers were dried and distilled to give 2.1 g (46%) of alcohol: bp 45–46 °C/35 mmHg (lit.[39] bp 136–137 °C); ^{1}H NMR δ 1.69 (d, 3 H, J = 6.2), 2.25 (q, 2 H, J = 6.2, 13), 3.63 (t, 2 H, J = 6.2), 5.35–5.65 (m, 2 H); IR 970, 1050, 3330 cm^{-1}.

(*E*)-1-Bromo-3-pentene was prepared from 1.2 g of (*E*)-3-penten-1-ol as described for 1-bromo-3-pentyne to give 740 mg (35%) of bromide: bp 124–128 °C (lit.[40] bp 122–128 °C); ^{1}H NMR δ 1.68 (d, 3 H, J = 6), 2.53 (q, 2 H, J = 6), 3.37 (t, 2 H, J = 7), 5.3–5.6 (m, 2 H).

(4*S*,4′*E*)-2-Oxo-3-(9-phenylfluoren-9-yl)-4-(1′-oxo-4′-hexenyl)oxazolidine (13). (*E*)-1-Bromo-3-pentene (600 mg, 4 mmol) in 4 mL of THF was added to 125 mg (5.2 mmol) of magnesium turnings and stirred for 40 min at room temperature. The solution was then transferred via cannula into a −78 °C solution of isoxazolidide **5** (430 mg, 1 mmol) in THF (10 mL). It was stirred for 15 min, then warmed to 0 °C, and stirred an additional 1.5 h before being transferred via Teflon tubing into a solution of 1 M NaH_2PO_4 (15 mL). The mixture was extracted with 25% isopropyl alcohol in $CHCl_3$ (3 × 10 mL), and the combined organic layer was washed with brine, dried, and evaporated to an oil which was chromatographed with a gradient of 25–100% EtOAc in hexane as eluant. Ketone **13** eluted first: 170 mg (40%); ^{1}H NMR δ 1.5 (m, 1 H), 1.59 (d, 3 H, J = 6.1), 1.83 (m, 1 H), 1.85 (m, 2 H), 3.88 (dd, 1 H, J = 4.3, 8.8), 4.1 (dd, 1 H, J = 4.3, 9.7), 4.29 (t, 1 H, J = 9), 5.14 (m, 1 H), 5.3 (m, 1 H), 7.2–7.75 (m, 13 H); ^{13}C NMR δ 206.4, 157.8, 146.4, 146.1, 140.2, 140.1, 139.9, 129.6, 129.4, 128.7, 128.66, 128.5, 128.46, 128.3, 127.5, 126.7, 126.3, 125.5, 120.1, 119.9, 72.7, 64.1, 62.6, 39.4, 25.7, 17.8. Isoxazolidide **5** (180 mg, 42%) was also recovered.

(4*S*)-2-Oxo-3-(9-phenylfluoren-9-yl)-4-(1′-oxopropyl)oxazolidine *tert*-Butyldimethylsilyl Enol Ether (14). 2,2,6,6-Tetramethylpiperidine (1.4 mmol, 240 μL) in THF (2 mL) at −78 °C was treated with *n*-butyllithium in hexane (1.5 M, 0.83 mL), warmed to 0 °C, stirred for 15 min, and added to a solution of ketone **7** (380 mg, 1 mmol) in 8 mL of THF at −78 °C. The solution was stirred for 1 h and then treated with 1 M *tert*-butyldimethylsilyl chloride (200 mg, 1.3 mmol) in THF (1 mL) which was pretreated with 100 mol % of Et_3N and centrifuged for 15 min to separate the Et_3N·HCl pellet before transferring via steel tubing into the enolate solution. The mixture was stirred for 1 h, at which time no silyl enol ether was detectable by TLC, 2.5 mL of DMPU was added, and the reaction was stirred an additional 30 min. Solvent was evaporated and the product was purified on silica gel with 3/1 hexane/EtOAc containing 1% Et_3N as eluant. Evaporation of the collected fractions gave a 3.8/1 *E*/*Z* mixture of **14** (340 mg, 69%). The ^{1}H NMR signals for the major *E* isomer include the following: δ 0.0 (s, 3 H), 0.1 (s, 3 H), 0.74 (d, 3 H, J = 7.2), 1.06 (s, 9 H), 4.13 (dd, 1 H, J = 8.2, 2.6), 4.21 (q, 1 H, J = 7.2), 4.56 (t, 1 H, J = 8.2), 4.75 (dd, 1 H, J = 2.6, 8.3), 7.35–7.85 (m, 12 H), 8.15 (m, 1 H). (*Z*)-**14** was prepared as above with potassium hexamethyldisilazide as base in neat THF at −78 °C to yield 420 mg (85%): mp 233–237 °C, $[\alpha]^{20}_D$ −240° (c 0.7, $CHCl_3$); ^{1}H NMR δ 0.0 (s, 3 H), 0.02 (s, 3 H), 1.02 (s, 9 H), 1.2 (d, 3 H, J = 6.9), 3.88 (q, 1 H, J = 6.9), 4.27 (m, 2 H), 4.58 (t, 1 H, J = 8.75), 7.4–8.3 (m, 13 H); ^{13}C NMR δ 157.8, 147.8, 146, 145.9, 141.7, 140.6, 140.3, 128.9, 128.8, 128.5, 128.4, 128.37, 127.7, 127.2, 126.2, 125, 119.9, 119.2, 104.1, 72.2, 66.5, 61.1, 25.7, 18.3, 11, −3.9, −4.2. Anal. Calcd for $C_{31}H_{35}NO_3Si$: C, 74.8; H, 7.1; N, 2.8. Found: C, 74.8; H, 7.1; N, 2.8.

General Procedure for Alkylation of Amino Ketones. A −78 °C solution of hexamethyldisilazane or 2,2,6,6-tetramethylpiperidine (1.75 mmol) in 2 mL of THF was treated with *n*-butyllithium (1.5 M in hexane, 1 mL, 1.5 mmol), stirred for 40 min at −78 °C, and transferred via stainless steel cannula into a −78 °C solution of amino ketone (1 mmol; see Table II for details) in 6 mL of THF at −78 °C. The solution was stirred for 1 h at −78 °C, and then either methyl iodide or 1-bromo-2-butyne (1.1 mmol) and DMEU (2 mL) were added. The mixture was stirred at 0 or −78 °C for the specified time, methanol (1 mL) was added, and the solution was partitioned between 10 mL of 1 M NaH_2PO_4 and 10 mL of Et_2O. The aqueous layer was extracted with Et_2O (3 × 10 mL), and the organic layers were combined, washed with water (3 × 10 mL), dried, and evaporated to a light yellow oil that was chromatographed on silica gel with 5% EtOAc in hexanes as eluant.

(4*S*,2′*R*)-3-(9-Phenylfluoren-9-yl)-4-(1′-oxo-2′-methyl-4′-hexynyl)oxazolidine (15): ^{1}H NMR δ 0.77 (d, 3 H, J = 7.0), 1.63 (t, 3 H, J = 2.4), 1.9 (m, 1 H), 2.1 (m, 1 H), 2.55 (m, 1 H), 3.35 (m, 1 H), 3.4 (m, 1 H), 3.65 (m, 1 H), 4.67 (d, 1 H, J = 6.8),

(38) This procedure is a modification of the preparation of *trans*-3-pentenal described in: Oppolzer, W.; Siles, S.; Snowden, R. L.; Bakker, B. H.; Petrzilka, M. *Tetrahedron* **1985**, *41*, 3497.

(39) Crombie, L.; Harper, S. H. *J. Chem. Soc.* **1950**, 873.

(40) Coates, R. M.; Senter, P. D.; Baker, W. R. *J. Org. Chem.* **1982**, *47*, 3597.

5.05 (d, 1 H, J = 6.6), 7.1–7.7 (m, 13 H). Anal. Calcd for $C_{29}H_{27}NO_2$: C, 82.6; H, 6.5; N, 3.3. Found: C, 82.2; H, 6.6; N, 3.2.

(4*S*,2′*S*)-3-(9-Phenylfluoren-9-yl)-4-(1′-oxo-2′-methyl-4′-hexynyl)oxazolidine (15): NMR δ 0.82 (d, 3 H, J = 7.0), 1.77 (t, 3 H, J = 2.3), 2.0 (m, 1 H), 2.2 (m, 1 H), 2.92 (m, 1 H), 3.16 (t, 1 H, J = 7.7), 3.4 (m, 1 H), 3.70 (m, 1 H), 4.6 (d, 1 H, J = 6.8), 5.03 (d, 1 H, J = 6.8), 7.2–7.8 (m, 13 H).

(4*S*,2′*R*)-2-Oxo-3-(9-phenylfluoren-9-yl)-4-(1′-oxo-2′-methyl-4′-hexynyl)oxazolidine (17): ^{1}H NMR δ 0.5 (d, 3 H, J = 6.8), 1.67 (t, 3 H, J = 2.4), 1.78 (m, 1 H), 1.98 (m, 1 H), 2.13 (m, 1 H), 4.14 (m, 1 H), 4.29 (m, 2 H), 7.2–7.8 (m, 13 H).

(4*S*,2′*S*)-2-Oxo-3-(9-phenylfluoren-9-yl)-4-(1′-oxo-2′-methyl-4′-hexynyl)oxazolidine (17): ^{1}H NMR δ 0.85 (d, 3 H, J = 7.2), 1.42 (m, 1 H), 1.66 (m, 1 H), 1.72 (t, 3 H, J = 2.3), 1.8 (m, 1 H), 3.88 (m, 1 H), 4.26 (m, 2 H), 7.2–7.8 (m, 13 H).

(4*S*,2′*S*)-2-Oxo-3-(9-phenylfluoren-9-yl)-4-(1′-oxo-2′-methyl-4′-hexynyl)oxazolidine (17). A −78 °C solution of hexamethyldisilazane (0.876 mL, 4.15 mmol) in 3.5 mL of THF was treated with n-butyllithium (1.5 M in hexane, 2.28 mL, 3.56 mmol), stirred for 20 min at 0 °C, and transferred via stainless steel cannula into a −78 °C solution of amino ketone **11** (1 g, 2.37 mmol) in 21.5 mL of THF. The solution was stirred for 1 h at −78 °C, and then methyl iodide (0.177 mL, 2.84 mmol) and DMEU (2.5 mL) were added. The mixture was warmed to 0 °C and stirred for 2 h, methanol (2 mL) and 10 mL of 1 M NaH_2PO_4 were added, and the aqueous layer was extracted with Et_2O (3 × 15 mL). The combined organic layer was washed with 0.5 M $Na_2S_2O_3$ (15 mL), water (3 × 10 mL), and brine, dried, and evaporated to 1.3 g of a foam. The ^{1}H NMR spectrum of the crude product showed a 20/1 anti/syn ratio of diastereomers. Crystallization from EtOAc/isooctane afforded 540 mg (53%) of **17** of 23/1 anti/syn composition. Chromatography of the mother liquor provided an additional 280 mg (27%) of **17** with 20/1 anti/syn composition: ^{1}H NMR δ 0.85 (d, 3 H, J = 7.2), 1.42 (m, 1 H), 1.66 (m, 1 H), 1.72 (t, 3 H, J = 2.3), 1.8 (m, 1 H), 3.88 (m, 1 H), 4.26 (m, 2 H), 7.2–7.8 (m, 13 H). Anal. Calcd for $C_{29}H_{25}NO_3$: C, 80; H, 5.8; N, 3.2. Found: C, 79.8; H, 5.8; N, 3.2. The melting point of (4*R*,2′*R*)-**17** (28/1 anti/syn) was 172–173 °C.

(*R*)-(−)-α-Methylhexanoic Acid (16). A 3.5/1 diastereomeric mixture of amino ketone **15** (700 mg, 1.66 mmol, ^{1}H NMR of major isomer shows methyl doublet at 0.77 ppm) was dissolved in acetic acid (10 mL), treated with 350 mg of 10 wt % palladium on carbon, and stirred for 2.5 h at room temperature under 1 atm of hydrogen. Water (4 mL) was added and the mixture was filtered through a pad of Celite which was washed with 2 × 8 mL of 3.5/1 acetic acid/water. The combined aqueous solution was treated with 3.8 g of lead tetraacetate, stirred for 6 h, and treated with 20 mL of 10% H_2SO_4. The mixture was filtered through Celite which was washed with water (20 mL), and the filtrate and washings were combined and extracted with Et_2O (5 × 20 mL). The combined organic phase was evaporated to an oil, which was partitioned between ether (30 mL) and saturated $NaHCO_3$ (10 mL). The organic phase was extracted with saturated $NaHCO_3$ (3 × 10 mL), and the basic washes were combined, cooled to 0 °C, acidified to pH 2 with concentrated HCl, and extracted with Et_2O (5 × 10 mL). The organic layers were washed with brine (10 mL), dried, and evaporated to yield 80 mg of **16** as an oil: $[\alpha]^{20}_D$ −8° (c 7.0, $CHCl_3$) (lit.[27] $[\alpha]^{20}_D$ −24.3 (neat)); NMR δ 0.9 (t, 3 H, J = 6.9), 1.17 (d, 3 H, J = 7), 1.3 (m, 4 H), 1.44 (m, 1 H), 1.68 (m, 1 H), 2.46 (hextet, 1 H, J = 7).

(4*S*,1′*S*,2′*S*)-2-Oxo-3-(9-phenylfluoren-9-yl)-4-(1′-hydroxy-2′-methyl-4′-hexynyl)oxazolidine (19). A solution of ketone **17** (700 mg, 1.61 mmol, 20/1 2′*S*/2′*R*) in 16 mL of THF at −78 °C was treated with a 0.91 M solution of $LiAlH_4$ in THF (1.86 mL, 1.69 mmol), stirred for 15 min, and quenched with 2 mL of a solution of $KHSO_4$ (500 mg) in 10 mL of H_2O. The mixture was partitioned between 15 mL of EtOAc and 10 mL of water, and the aqueous layer was extracted with 3 × 15 mL of EtOAc. The combined organic layer was washed with brine, dried, and evaporated to 730 mg of a white foam. Chromatography, eluting with a gradient of 0–10% EtOAc in hexane, gave 20 mg (3%) of (4*S*,1′*S*,2′*R*)-**19** (^{1}H NMR δ 0.71 (d, 3 H, J = 6.8), 1.0 (m, 1 H), 1.22 (m, 1 H), 1.3 (m, 1 H), 1.6 (t, 3 H, J = 2.3), 1.87 (br s, 1 H), 2.82 (d, 1 H, J = 4.8), 3.96 (t, 1 H, J = 6), 4.3 (m, 2 H), 7.1–7.7 (m, 12 H), 8.1 (m, 1 H); ^{13}C NMR δ 157.8, 147.9, 145.2, 141.5, 140.2, 139.2, 129.4, 129.2, 129, 128.5, 128.1, 128, 127.3, 126.3, 124.7, 120.5, 119.9, 77.9, 77.1, 72.6, 71.9, 63.9, 59.9, 30.9, 25.9, 12.1, 3.3) followed by (4*S*,1′*S*,2′*S*)-**19** (590 mg, 84%, >97% de) (mp 154–155 °C; ^{1}H NMR δ 0.38 (d, 3 H, J = 6.9), 1.25 (m, 1 H), 1.7 (t, 3 H, J = 2.3), 1.85 (m, 1 H), 2 (m, 1 H), 2.1 (d, 1 H, J = 4), 2.81 (m, 1 H), 4.2 (m, 1 H), 4.34 (d, 1 H, J = 9.2), 4.5 (dd, 1 H, J = 8.8, 8.5), 7.2–8.2 (m, 13 H); ^{13}C NMR δ 157.7, 147.7, 145.1, 141.7, 140.1, 139.4, 129.3, 129, 128.8, 128.4, 128, 127.8, 127.2, 126.3, 124.6, 120.3, 119.7, 77.8, 77.3, 74.8, 72.1, 64.9, 59.9, 32.1, 20.6, 17.4, 3.3. Anal. Calcd for $C_{29}H_{27}NO_3$: C, 79.6; H, 6.2; N, 3.2. Found: C, 79.2; H, 6.3; N, 3.1.

(4*R*,1′*R*,2′*R*)-2-Oxo-3-(9-phenylfluoren-9-yl)-4-(1′-hydroxy-2′-methyl-4′-hexynyl)oxazolidine (19) from (*R*)-10. To hexamethyldisilazane (3.69 mL, 17.5 mmol) in 10 mL of THF at 0 °C was added n-butyllithium (1.5 M in hexane, 10 mL, 15 mmol), and the solution was stirred for 30 min at 0 °C and then transferred via stainless steel cannula into a −78 °C solution of amino ketone **10** (4.22 g, 10 mmol) in 80 mL of THF. The flask that contained the LiHMDS solution was rinsed with 2 mL of THF that was similarly transferred into the enolate solution, which was then stirred at −78 °C for 1 h. Methyl iodide (747 μL, 12 mmol) and DMEU (10 mL) were added simultaneously, and the mixture was warmed to 0 °C and stirred for 2 h. Methanol (2 mL), 1 M KH_2PO_4 (12 mL), and water (20 mL) were added. The aqueous layer was extracted with Et_2O (3 × 50 mL), and the combined organic layer was washed with 0.5 M $Na_2S_2O_3$ (50 mL), water (3 × 40 mL), and brine (50 mL), dried, and evaporated to 5.3 g of **17** as a foam. The ^{1}H NMR spectrum of the crude product showed a 20/1 anti/syn ratio of diastereomers and 85–90% completion.

The foam was redissolved in 100 mL of THF, cooled to −78 °C, and treated with 1.4 M solution of $LiAlH_4$ (7.9 mL, 11 mmol) in THF. After stirring for 15 min, the −78 °C solution was treated with a solution of $KHSO_4$ (750 mg) in 15 mL of H_2O. The mixture was partitioned between 50 mL of EtOAc and 50 mL of H_2O, and the aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic phase was washed with brine, dried, and evaporated to a white foam (5 g), which was first chromatographed on silica gel with a 0–10% gradient of EtOAc/hexane as eluant. The mixed fractions were further purified by either recrystallization or medium-pressure liquid chromatography to give 3.2 g (73% of a >98/2 anti/syn mix) of (4*R*,1′*R*,2′*R*)-**19** (mp 154–155 °C), 18 mg (4% of a 1/26 anti/syn mix) of (4*R*,1′*R*,2′*S*)-**19**, and 560 mg (13%) of (4*R*,1′*R*)-2-oxo-3-(9-phenylfluoren-9-yl)-4-(1′-hydroxy-4′-hexynyl)oxazolidine (**40**): $[\alpha]^{20}_D$ +606° (c 1.1, $CHCl_3$); ^{1}H NMR δ 1.2 (m, 4 H), 1.67 (t, 3 H, J = 2.3), 2.4 (d, 1 H, J = 2.9), 2.85 (m, 1 H), 3.94 (q, 1 H), 4.33 (m, 2 H), 7.18–7.8 (m, 12 H), 8.15 (m, 1 H). Anal. Calcd for $C_{28}H_{25}NO_3$: C, 79.4; H, 6; N, 3.3. Found: C, 79.2; H, 6.3; N, 3.2.

(4*S*,5*S*,1′*S*)-2-Oxo-4-(1′-methyl-3′-pentynyl)-5-(*N*-(9-phenylfluoren-9-yl)amino)dioxane (20). A 0 °C solution of alcohol **19** (730 mg, 1.67 mmol) in 17 mL of THF was treated with 1.1 mL of a 1.8 M potassium hexamethyldisilazide solution in THF, stirred for 15 min, treated with methoxymethyl chloride (120 μL, 2 mmol), and stirred for an additional 15 min. The solution was quenched with 10 mL of 1 M NaH_2PO_4 and extracted with 3 × 10 mL of EtOAc. The combined organic extracts were washed with brine, dried, and evaporated to an oil which was chromatographed with 25% EtOAc in hexane as eluant. Evaporation of the collected fractions yielded 540 mg (74%) of **20**: ^{1}H NMR δ 1.14 (d, 3 H, J = 6.7), 1.2 (m, 1 H), 1.73 (t, 3 H, J = 2), 2.09 (m, 1 H), 2.26 (m, 1 H), 2.38 (m, 1 H), 2.75 (m, 2 H), 3.7 (br d, 1 H, J = 2.2), 4.21 (dd, 1 H, J = 7.1, 2.4), 7.1–8.1 (m, 13 H); ^{13}C NMR δ 157.2, 148.5, 145.2, 141.3, 140, 139, 129.7, 129.2, 129.1, 128.4, 128.1, 127.2, 127, 125.8, 124.6, 120.6, 120.4, 79.1, 77.7, 75.9, 71.5, 62.3, 59.6, 36.2, 21.6, 14.3, 3.4.

(2*S*,3*S*,4*S*)-2-(*N*-(9-Phenylfluoren-9-yl)amino)-3-hydroxy-4-methyl-6-octynol (22). Alcohol **19** (2 g, 4.58 mmol) was dissolved in 95 mL of 1 M ethanolic potassium hydroxide, and the solution was stirred at reflux for 18 h, cooled, and partitioned between 2/1 H_2O/brine (90 mL) and EtOAc (60 mL). The aqueous phase was extracted with 3 × 25 mL of EtOAc, and the combined organic extracts were washed with brine, dried, and evaporated to an oil which was chromatographed with 25% EtOAc in hexane as eluant. Evaporation of the collected fractions yielded 1.69 g (90%) of **22** as an oil which eventually solidified: mp 97–104

°C; $[\alpha]^{20}_D$ −65° (c 2.5, $CHCl_3$); ^1H NMR δ 0.62 (d, 3 H, J = 6.7), 1.64 (m, 1 H), 1.7 (t, 3 H, J = 2.2), 1.98 (m, 2 H), 2.24 (t, 1 H, J = 3.5), 2.77 (dd, 1 H, J = 4, 11.2), 2.95 (br s, 2 H), 3.12 (d, 1 H, J = 11.1), 3.31 (dd, 1 H, J = 6.8, 4.7), 7.15–7.8 (m, 13 H); ^{13}C NMR δ 150.7, 148.8, 144.7, 140.34, 140.31, 129.8, 129.1, 128.5, 128.3, 128, 127.3, 125.9, 125.7, 124.7, 120, 119.9, 79.1, 76.6, 72, 64, 53.3, 34.5, 20.8, 16.6, 3.5. Anal. Calcd for $C_{28}H_{29}NO_2$: C, 81.7; H, 7.1; N, 3.4. Found: C, 82.0; H, 7.0; N, 3.3.

(2*S*)-2-(*N*-Methyl-*N*-(9-phenylfluoren-9-yl)amino)-3-hydroxy-4-methyl-6-octyn-1-ol (21) and (2*S*)-2-(*N*-(9-Phenylfluoren-9-yl)amino)-3-hydroxy-4-methyl-6-octyn-1-ol (22). Ketone **17** (530 mg, 1.2 mmol) in 9 mL of THF was added to a suspension of $LiAlH_4$ (144 mg, 3.6 mmol) in 9 mL of THF at −78 °C. The mixture was stirred 30 min and then warmed to 30 °C for 2 h, $LiAlH_4$ (40 mg, 1 mmol) was added, and the solution was heated to 40–45 °C for 50 min. The solution was cooled to 0 °C, quenched slowly with aqueous $KHSO_4$ (2 g in 15 mL of H_2O), and filtered, and the filter cake was washed with EtOAc (20 mL). The combined organic solution was washed with brine, dried, and evaporated to an oil which was chromatographed, eluting with a gradient of 25–50% EtOAc in hexane. Diol **21** (180 mg, 35%) was eluted first: ^1H NMR δ 0.43 (d, 3 H, J = 6.6), 0.49 (m, 1 H), 1.56 (q, 1 H, J = 7), 1.72 (t, 3 H, J = 2.4), 2.2 (m, 2 H), 2.55 (m, 1 H), 2.66 (s, 3 H), 2.97 (m, 1 H), 3.27 (m, 1 H), 3.7 (br d, 1 H, J = 9.8), 4.43 (br s, 1 H), 7.2–7.8 (m, 13 H). Anal. Calcd for $C_{29}H_{31}NO_2$: C, 81.8; H, 7.3; N, 3.3. Found: C, 81.6; H, 7.4; N, 3.2. Diol **22** (170 mg, 34%) eluted next: ^1H NMR δ 0.58 (d, 3 H, J = 6.7), 0.85 (m, 1 H), 1.54 (m, 1 H), 1.7 (t, 3 H, J = 2.4), 1.98 (m, 2 H), 2.12 (m, 1 H), 2.67 (dd, 1 H, J = 3.8, 11.1), 3.52 (dd, 1 H, J = 4.1, 7.1), 7.1–7.8 (m, 13 H).

(2*S*)-2-(*N*-Methyl-*N*-(9-phenylfluoren-9-yl)amino)-3-hydroxypentan-1-ol (23), (2*S*)-2-(*N*-(9-Phenylfluoren-9-yl)amino)-3-hydroxypentan-1-ol (24), and (2*S*)-2-(*N*-(9-Phenylfluoren-9-yl)amino)pentan-3-ol (25). Ketone **7** (1 g, 2.6 mmol) in 20 mL of THF was added to a suspension of $LiAlH_4$ (400 mg, 10 mmol) in 20 mL of THF at −78 °C. The mixture was stirred for 45 min, warmed to a reflux for 30 min, cooled to −78 °C, quenched slowly with aqueous $KHSO_4$ (2 g in 20 mL of H_2O), and filtered through Celite, and the filter cake was washed with EtOAc (2 × 20 mL). The combined solution was washed with brine (40 mL), dried, and evaporated to an oil which was chromatographed with a gradient of 25–50% EtOAc in hexane as eluant. Alcohol **25** (250 mg, 28%) was first to elute: ^1H NMR δ 0.54 (d, 3 H, J = 6.4), 0.77 (t, 3 H, J = 7.4), 1.08 (m, 1 H), 1.37 (m, 1 H), 2.05 (dq, 1 H, J = 0.9, 6.4), 2.84 (br s, 1 H), 3.02 (dt, 1 H, J = 3.3, 7.8), 7.1–7.8 (m, 13 H). The desired *N*-methylamino diol **23** (250 mg, 26%) eluted next: ^1H NMR δ 0.84 (t, 3 H, J = 7.2), 1.1 (m, 1 H), 1.5 (m, 1 H), 2.4 (m, 1 H), 2.67 (s, 3 H), 3.0 (br m, 1 H), 3.26 (m, 1 H), 3.5 (m, 1 H), 4.5 (br s, 1 H), 7.2–7.9 (m, 13 H). Diol **24** (220 mg, 24%) eluted last: ^1H NMR δ 0.67 (t, 3 H), 1.25 (m, 1 H), 1.36 (m, 1 H), 2.03 (m, 1 H), 2.76 (dd, 1 H), 2.9 (br s, 1 H), 3.1 (dd, 1 H), 3.4 (m, 1 H), 7.2–7.75 (m, 13 H).

(4*S*,5*S*)-3-(9-Phenylfluoren-9-yl)-4-(hydroxymethyl)-5-ethyloxazolidine (27). A solution of amino ketone **11** (450 mg, 1.2 mmol) in 12 mL of THF at −78 °C was treated with 1.1 mL of 1.1 M $LiAlH_4$ in THF, stirred for 15 min, and quenched with $KHSO_4$ (0.5 g) in 10 mL of water. The mixture was extracted with EtOAc (3 × 10 mL), and the combined organic extracts were washed with brine, dried, and evaporated to an oil which was chromatographed with 25% EtOAc in hexane as eluant. Evaporation of the collected fractions yielded 430 mg of **27** (97%): mp 188–189 °C; $[\alpha]^{20}_D$ −460° (c 2.3, $CHCl_3$); ^1H NMR δ 0.63 (t, 3 H, J = 7.4), 0.95 (m, 2 H), 2.1 (m, 1 H), 2.45 (dd, 1 H, J = 3.3, 8.7), 2.95 (m, 1 H), 3.1 (m, 1 H), 3.6 (m, 1 H), 4.65 (d, 1 H, J = 7.2), 5.07 (d, 1 H, J = 7.1), 7.1–7.8 (m, 13 H); ^{13}C NMR 148.9, 145.6, 144.3, 141.8, 138.9, 128.8, 128.6, 128.4, 127.8, 127.72, 127.69, 127.4, 126.8, 125.2, 119.9, 119.3, 84.7, 82.0, 77.2, 63.6, 62.7, 25.4, 10.2. Anal. Calcd for $C_{25}H_{25}NO_2$: C, 80.8; H, 6.8; N, 3.8. Found: C, 80.9; H, 6.8; N, 3.8.

General Procedure for the Oxidation of *N*-(PhFl)Amino Alcohols to *N*-(PhFl)Amino Aldehydes and *N*-(PhFl)Amino Ketones.[20] Dimethyl sulfide (0.65 mL, 8.5 mmol) was added to a suspension of *N*-chlorosuccinimide (910 mg, 6.8 mmol) in 20 mL of toluene at 0 °C and stirred for 20 min when a white precipitate was observed. The mixture was cooled to −25 °C and amino alcohol **27**, **32**, or **40** (3.4 mmol) in 6 mL of toluene was added to the cooled suspension, which was then stirred for 5 h at −25 °C. Triethylamine (1.18 mL, 8.5 mmol) was added to the mixture, which was stirred for 10 min at −25 °C and then warmed to room temperature for an additional 10 min. Water (25 mL) was added, the layers were separated, and the aqueous layer was extracted with EtOAc (3 × 25 mL). The combined organic layer was washed with brine, dried, and evaporated to a solid which was chromatographed with a gradient of 0–25% EtOAc in hexane as eluant.

(4*R*,5*S*)-3-(9-Phenylfluoren-9-yl)-5-ethyloxazolidine-4-carboxaldehyde (28): yield 73%; mp 183 °C; $[\alpha]^{20}_D$ −403° (c 1.0, $CHCl_3$); ^1H NMR δ 0.62 (t, 3 H, J = 7.4), 1.1 (m, 2 H), 2.4 (dd, 1 H, J = 2.9, 7.4), 3.7 (q, 1 H, J = 7, 12.1), 4.75 (d, 1 H, J = 6.7), 5.07 (d, 1 H, J = 6.6), 7.1–7.8 (m, 13 H), 9.45 (d, 1 H, J = 2.9); ^{13}C NMR δ 201.6, 148.8, 145.6, 143.5, 141.9, 138.9, 129.1, 128.8, 128.6, 128, 127.9, 127.6, 127.1, 127, 125.3, 120.1, 119.7, 84.3, 79.7, 76.8, 70.2, 25.4, 9.6. Anal. Calcd for $C_{25}H_{23}NO_2$: C, 81.3; H, 6.3; N, 3.8. Found: C, 81; H, 6.3; N, 3.8. Amino ketone **11** (6%) was also obtained.

(4*R*,5*S*,1′*S*)-3-(9-Phenylfluoren-9-yl)-5-(1′-methyl-3′-pentynyl)oxazolidine-4-carboxaldehyde (34): yield 62%; mp 113.5–114 °C; $[\alpha]^{20}_D$ −381° (c 0.4, $CHCl_3$); ^1H NMR δ 0.57 (d, 3 H, J = 6.9), 0.88 (m, 1 H), 1.7 (t, 3 H, J = 2.4), 1.88 (m, 2 H), 2.55 (dd, 1 H, J = 2.7, 6.7), 3.7 (t, 1 H, J = 7.3), 4.69 (d, 1 H, J = 7), 5.04 (d, 1 H, J = 6.9), 7.1–7.75 (m, 13 H), 9.45 (d, 1 H, J = 2.7); ^{13}C NMR δ 200.5, 148.7, 145.7, 143.5, 141.8, 138.9, 129.2, 128.8, 128.6, 128.1, 127.8, 127.6, 127.3, 126.9, 125.4, 120, 119.7, 84.1, 80.9, 76.8, 76.4, 68.7, 35.2, 22, 15.3, 3.4. Anal. Calcd for $C_{29}H_{27}NO_2$: C, 82.6; H, 6.5; N, 3.3. Found: C, 82.5; H, 6.6; N, 3.3. Alcohol **32** (26%) was also recovered.

Aldehyde (4*S*,5*R*,1′*R*)-34 was obtained in identical yields: mp 113–113.5 °C; $[\alpha]^{20}_D$ +383° (c, 1.3, $CHCl_3$). Stirring the reaction mixture 6 h provided a 79% yield of **34** with 6% of (methylthio)methyl ether **35**: ^1H NMR δ 0.41 (m, 1 H), 0.58 (d, 3 H, J = 6.8), 1.72 (t, 3 H, J = 2.4), 1.78 (m, 1 H), 1.85 (m, 1 H), 2.06 (s, 3 H), 2.28 (m, 1 H), 3.28 (dd, 1 H, J = 4.8, 9.7), 3.4 (m, 2 H), 4.4 (d, 1 H, J = 11.3), 4.48 (d, 1 H, J = 11.3), 4.68 (d, 1 H, J = 7.3), 4.99 (d, 1 H, J = 7.3), 7.17–7.7 (m, 13 H); ^{13}C NMR δ 149, 147, 144.7, 141.6, 139, 128.8, 128.4, 128.2, 128, 127.6, 127.5, 127.2, 127, 126, 120, 119.6, 119.4, 84, 83.7, 77.3, 76.7, 76.2, 75, 70.4, 60.6, 35.2, 22, 16.2, 13.7, 3.6.

(4*R*)-2-Oxo-3-(9-phenylfluoren-9-yl)-4-(1′-oxo-4′-hexynyl)oxazolidine (10) was obtained via oxidation of alcohol **40** in 83% yield. (Methylthio)methyl ether **41** was also isolated in 2% yield: ^1H NMR δ 0.88 (m, 1 H), 1.2 (m, 1 H), 1.25 (m, 2 H), 1.7 (t, 3 H, J = 2.4), 1.91 (s, 3 H), 2.61 (m, 1 H), 3.37 (d, 1 H, J = 11.7), 3.93 (d, 1 H, J = 11.7), 4.08 (m, 1 H), 4.26 (m, 1 H), 4.36 (t, 1 H, J = 8.4), 7.2–7.8 (m, 12 H), 8.18 (m, 1 H).

(4*R*,5*S*)-Methyl 3-(9-Phenylfluoren-9-yl)-5-ethyloxazolidine-4-carboxylate (29). A solution of $NaClO_2$ (1.8 g, 20 mmol, 80% by weight) and NaH_2PO_4 (2.5 g, 18 mmol) in 10 mL of water was added to aldehyde **28** (750 mg, 2 mmol) in 40 mL of 1/1 acetonitrile/*tert*-butyl alcohol. The solution was stirred for 15 min at room temperature and then partitioned between 50 mL of 1 M H_3PO_4 and 40 mL of ether, and the aqueous layer was extracted with 3 × 40 mL of ether. The combined organic phase was washed with brine and then treated with excess 0.25 M diazomethane in ether (10 mL), the excess then being consumed by addition of acetic acid (200 μL). The solution was dried and evaporated to an oil which was chromatographed with a gradient of 10–25% EtOAc in hexane as eluant. Evaporation of the collected fractions gave 580 mg (73%) of ester **29**: mp 161–162 °C; $[\alpha]^{20}_D$ −344° (c 1.2, $CHCl_3$); ^1H NMR δ 0.62 (t, 3 H, J = 7.4), 1.1 (m, 2 H), 2.6 (d, 1 H, J = 7.4), 3.4 (s, 3 H), 3.7 (q, 1 H, J = 7, 12), 4.85 (d, 1 H, J = 6.7), 5.03 (d, 1 H, J = 6.7), 7.1–7.8 (m, 13 H); ^{13}C NMR δ 174.1, 148.8, 146.3, 144.1, 141.9, 138.8, 128.8, 128.5, 128.3, 127.8, 127.6, 127.4, 127.1, 127, 126, 119.8, 119.5, 84.5, 83.5, 77.2, 65.4, 51.6, 25.6, 9.6. Anal. Calcd for $C_{26}H_{25}NO_3$: C, 78.2; H, 6.3; N, 3.5. Found: C, 77.9; H, 6.3; N, 3.4.

(2*R*,3*S*)-Methyl 2-(*N*-(9-Phenylfluoren-9-yl)-*N*-methylamino)-3-hydroxypentanoate (30). A solution of oxazolidine **29** (100 mg, 0.25 mmol) in 0.2 M HCl in THF was treated with $NaCNBH_3$ (50 mg, 0.8 mmol), stirred for 20 min, and quenched with $NaHCO_3$ (3 mL). The mixture was extracted with 3 × 4 mL of EtOAc, and the combined organic layer was washed with brine, dried, and evaporated to an oil that was chromatographed with

a gradient of 0–25% EtOAc in hexane as eluant. Evaporation of the collected fractions gave 90 mg (90%) of ester **30**: mp 104–106 °C; $[\alpha]^{20}_D$ +449° (*c* 0.8, $CHCl_3$); ^1H NMR δ 0.82 (t, 3 H, *J* = 7.4), 1.07 (m, 1 H), 1.2 (m, 1 H), 2.8 (s, 3 H), 2.9 (s, 3 H), 3 (d, 1 H, *J* = 9.8), 3.77 (m, 1 H), 3.89 (s, 1 H), 7.1–7.8 (m, 13 H); ^{13}C NMR δ 170.8, 147.4, 144.9, 142.6, 142, 139.4, 128.6, 128.5, 128.4, 128.2, 127.5, 127.1, 127, 126.7, 126.5, 125.4, 120.5, 120, 77.8, 68.5, 63.1, 50.9, 31.6, 26.1, 9.4. Anal. Calcd for $C_{26}H_{27}NO_3$: C, 77.8; H, 6.8; N, 3.5. Found: C, 77.7; H, 7.0; N, 3.4.

(4*S*,5*S*,1′*S*)-3-(9-Phenylfluoren-9-yl)-4-(hydroxymethyl)-5-(1′-methyl-3′-pentynyl)oxazolidine (32). A solution of diol **22** (1.69 g, 4.11 mmol), toluenesulfonic acid (25 mg), and 1.7 mL of 37% aqueous formaldehyde (20.4 mmol) in THF (40 mL) was stirred for 24 h, then diluted with 25 mL of EtOAc, washed with 20 mL of $NaHCO_3$ and 20 mL of brine, dried, and evaporated to an oil which was chromatographed on silica gel with a gradient of 25–75% EtOAc in hexane as eluant. Evaporation of the collected fractions yielded 1.59 g (91%) of **32** as a foam: $[\alpha]^{20}_D$ +406° (*c* 0.8, $CHCl_3$); ^1H NMR δ 0.61 (d, 3 H, *J* = 4.8), 0.64 (m, 1 H), 1.65 (m, 1 H), 1.71 (t, 3 H, *J* = 2.5), 1.85 (m, 1 H), 2.24 (m, 1 H), 2.4 (br s, 1 H), 3 (dd, 1 H, *J* = 6.7, 11), 3.2 (m, 1 H), 3.42 (t, 1 H, *J* = 7), 4.65 (d, 1 H, *J* = 7.4), 5.07 (d, 1 H, *J* = 7.3), 7.2–7.8 (m, 13 H); ^{13}C NMR δ 148.8, 146.5, 144.2, 141.6, 139, 128.9, 128.5, 128.45, 127.9, 127.8, 127.6, 127.4, 126.8, 125.2, 119.9, 119.4, 84.3, 83.1, 76.8, 76.5, 63.4, 62.5, 35, 24.7, 21.9, 16, 3.5. Anal. Calcd for $C_{29}H_{29}NO_2$: C, 82.2; H, 6.9; N, 3.3. Found: C, 81.9; H, 6.9; N, 3.2. Less substituted oxazolidine **33** (25 mg, 1.4%) was also isolated: ^1H NMR δ 0.83 (d, 3 H, *J* = 6.9), 1.3 (m, 1 H), 1.6 (t, 3 H, *J* = 2.3), 1.7 (m, 2 H), 2.85 (m, 2 H), 3.26 (m, 2 H), 3.66 (bs, 1 H), 4.76 (d, 1 H, *J* = 7.1), 5.1 (d, 1 H, *J* = 7.1), 7.2–7.8 (m, 13 H).

(4*R*,5*S*,1′*S*)-3-(9-Phenylfluoren-9-yl)-5-(1′-methyl-3′-pentynyl)oxazolidine-4-carboxylic Acid (36). A 0 °C solution of aldehyde **34** (500 mg, 1.19 mmol) in 1/1/0.25 acetonitrile/*tert*-butyl alcohol/2-methyl-2-butene (27 mL) was treated with a solution of $NaClO_2$ (1.09 g, 12 mmol, 80 wt %) and NaH_2PO_4 (1.38 g, 9.5 mmol) in 7.6 mL of H_2O over 5 min and then stirred for an additional 5 min. The aqueous layer was separated and extracted with 2 × 10 mL of EtOAc, and the combined organic extracts were washed with 20 mL of 1 M $Na_2S_2O_4$ and 10 mL of brine, dried, and evaporated to an oil which was crystallized from EtOAc/hexane to yield 490 mg (94%) of acid **36**: mp 180–180.5 °C dec; $[\alpha]^{20}_D$ −319° (*c* 0.8, $CHCl_3$); ^1H NMR δ 0.64 (m, 1 H), 0.71 (d, 3 H, *J* = 6.3), 1.71 (t, 3 H, *J* = 2.5), 1.76–1.91 (m, 2 H), 2.76 (d, 1 H, *J* = 6.1), 3.64 (t, 1 H, *J* = 6.8), 4.73 (d, 1 H, *J* = 7.3), 5.15 (d, 1 H, *J* = 7.3), 7.15–7.8 (m, 13 H); ^{13}C NMR δ 174, 147.3, 145.2, 142.6, 141.7, 138.9, 129.6, 129.1, 128.9, 128.5, 127.9, 127.85, 127.7, 126.6, 125.2, 120.2, 119.8, 84.7, 83.4, 76.8, 76.6, 64.9, 60.4, 35.4, 21.7, 15.8, 3.5. Anal. Calcd for $C_{29}H_{27}NO_3$: C, 79.6; H, 6.2; N, 3.2. Found: C, 79.4; H, 6.2; N, 2.9.

(2*S*,3*R*,4*R*)-2-(*N*-(9-Phenylfluoren-9-yl)-*N*-methylamino)-3-hydroxy-4-methyl-6-octynoic Acid (37). A solution of $NaCNBH_3$ (503 mg, 8 mmol) in 10 mL of THF was treated with acid **36** (438 mg, 1 mmol) and cooled to 0 °C. Trifluoroacetic acid (231 μL, 3 mmol) was added, and the solution was stirred 20 min and then quenched with saturated $NaHCO_3$ (10 mL). The mixture was extracted with 3 × 15 mL of EtOAc, and the organic extracts were washed with brine, dried, and evaporated onto 5 g of silica gel. Chromatography of the resulting powder with 25–100% EtOAc in hexane as eluant yielded 421 mg (96%) of **37**: ^1H NMR δ 1.07 (d, 3 H, *J* = 6.9), 1.44 (m, 1 H), 1.7 (t, 3 H, *J* = 2.4), 1.76 (m, 1 H), 1.86 (m, 1 H), 2.76 (s, 3 H), 3.18 (d, 1 H, *J* = 10), 3.75 (dd, 1 H, *J* = 2.6, 10), 7.15–7.75 (m, 13 H); ^{13}C NMR δ 175.4, 147, 145.1, 142.1, 142, 139.7, 129, 128.6, 128, 127.6, 126.6, 126.5, 125.3, 120.2, 78.2, 78, 76.2, 70.5, 61, 35, 31.4, 18.8, 17.7, 3.5. Anal. Calcd for $C_{29}H_{29}NO_3$: C, 79.2; H, 6.7; N, 3.2. Found: C, 78.9; H, 6.7; N, 3.1.

(2*S*,3*R*,4*R*,6*Z*)-2-(*N*-(9-Phenylfluoren-9-yl)-*N*-methylamino)-3-hydroxy-4-methyl-6-octenoic Acid (39). Lindlar's catalyst (9 mg, Alpha Chemicals) and a solution of acid **37** (88 mg, 0.2 mmol) in methanol (2 mL) were stirred under 1 atm of hydrogen for 24 h and then filtered through a pad of Celite. The pad was washed with 2 × 5 mL of EtOAc, and the combined solution was evaporated to a foam (85 mg) which was chromatographed with 25% EtOAc in hexane as eluant. First to elute was **39** (60 mg, 68%): $[\alpha]^{20}_D$ −341° (*c* 0.7, $CHCl_3$); ^1H NMR δ 0.98 (d, 3 H, *J* = 6.9), 1.23 (m, 1 H), 1.44 (d, 3 H, *J* = 6.8), 1.57 (m, 1 H), 1.78 (m, 1 H), 2.76 (s, 3 H), 3.23 (d, 1 H, *J* = 10.1), 3.73 (dd, 1 H, *J* = 2, 10.1), 5.23 (m, 1 H), 5.4 (m, 1 H), 7.18–7.75 (m, 13 H); ^{13}C NMR δ 175.7, 147.1, 145.1, 142.1, 142, 139.7, 129, 128.8, 128.6, 128.1, 127.6, 126.65, 126.57, 126.54, 125.4, 124.8, 120.2, 120.1, 78, 71.4, 60.8, 35.3, 31.4, 26.4, 17.5, 12.7. Anal. Calcd for $C_{29}H_{31}NO_3$: C, 78.9; H, 7.1; N, 3.2. Found: C, 78.9; H, 7.2; N, 3.1. Acid **36** (10 mg, 11%) was also recovered.

(2*S*,3*R*,4*R*,6*E*)-3-Hydroxy-4-methyl-2-(methylamino)-6-octenoic Acid (L-MeBmt, L-1). To a −78 °C blue solution of 83 mg of lithium metal (12 mmol) in 50 mL of ammonia (distilled from lithium) was added **37** (264 mg, 0.6 mmol) in THF (6 mL). The mixture was kept at reflux with a −20 °C bath for 2 min, cooled to −78 °C, and quenched with 2 mL of distilled H_2O, and the volatiles were allowed to evaporate overnight. The residue was dissolved in 16 mL of H_2O and washed with 3 × 15 mL of isooctane and 3 × 15 mL of Et_2O. The pH was adjusted to 5.5 with 1 M HCl, and the aqueous phase was evaporated to a solid which was purified on a BioRad AG 1-X8 anion-exchange resin (hydroxide form, 10 g) with 0–0.5 M acetic acid as eluant. Evaporation of the ninhydrin-positive fractions gave 92 mg (76%) of **1**: ^1H NMR (D_2O, NaOD, TPS, δ = 0) δ 0.88 (d, 3 H, *J* = 6.8), 1.65 (d, 3 H, *J* = 5), 1.67 (m, 1 H), 1.84 (m, 2 H), 2.27 (s, 3 H), 2.3 (br m, 1 H), 3.07 (d, 1 H, *J* = 4.7), 3.49 (q, 1 H, *J* = 4.9, 6.7), 5.53 (m, 2 H); ^1H NMR (D_2O, CF_3CO_2H, dioxane, δ = 3.53) δ 0.72 (d, 3 H, *J* = 6.8), 1.43 (d, 3 H, *J* = 5.9), 1.55 (m, 1 H), 1.7 (m, 1 H), 2.07 (br m, 1 H), 2.59 (s, 3 H), 3.7 (q, 1 H, *J* = 4.2, 7.8), 3.92 (d, 1 H, *J* = 4.1), 5.53 (m, 2 H); mp 233 °C (lit.[10] mp 240–241 °C) after recrystallization from EtOH/H_2O; $[\alpha]^{20}_D$ +12.2° (*c* 0.55, H_2O, pH 7, phosphate–hydroxide buffer) (lit.[10] $[\alpha]^{20}_D$ +13.5 (*c* 0.5, H_2O, pH 7, phosphate–Titrisol Merck buffer). Anal. Calcd for $C_{10}H_{19}NO_3$: C, 59.7; H, 9.5; N, 7.0. Found: C, 59.3; H, 9.1; N, 6.9.

(2*R*,3*S*,4*S*,6*E*)-MeBmt (D-1): mp 232 °C; $[\alpha]^{20}_D$ −11.2° (*c* 0.5, H_2O, pH 7, phosphate–hydroxide buffer).

Preparation of Diastereomeric Amides 38 and 43 for Optical Purity Studies. A 0 °C solution of 0.08 mmol of L- and D-*N*-PhFl-MeBmt triple-bond analogue **37** or L-oxazolidine acid **42** [prepared from **1** by refluxing in acetone for 24 h;[6] ^1H NMR (pyridine-d_5, TMS) δ 1.06 (d, 3 H, *J* = 6.7), 1.23 (s, 3 H), 1.26 (m, 1 H), 1.5 (s, 3 H), 1.58 (d, 3 H, *J* = 4.6), 2.05 (m, 2 H), 2.46 (s, 3 H), 3.55 (m, 1 H), 4.36 (m, 1 H), 5.49 (m, 2 H)], hydroxybenzotriazole (300–500 mol %), and either (*R*)-(+)- or (*R*,*S*)-(±)-α-methylbenzylamine (20 μL, 0.16 mmol, 200 mol %) in THF (1 mL) was treated with dicyclohexylcarbodiimide (26 mg, 0.13 mmol, 150 mol %) and stirred at 0 °C for 30 h. The mixture was filtered through a plug of silica gel with 50% EtOAc in hexane as eluant, the solvent was evaporated, and the residue was resubjected to the reaction conditions until complete consumption of the amino acid. In the case of **43**, the crude residue was used directly for doping experiments. Amides **38** were assayed for diastereomeric purity after further purification on a 50-μm plate of silica gel which provided each in 44% yield.

(2*S*,3*R*,4*R*)-2-(*N*-(9-Phenylfluoren-9-yl)-*N*-methylamino)-3-hydroxy-4-methyl-6-octynoic Acid (*R*)-α-Methylbenzylamide (L-(*R*)-38): ^1H NMR δ 1.06 (d, 3 H, *J* = 7), 1.18 (m, 1 H), 1.2 (d, 3 H, *J* = 6.8), 1.46 (t, 3 H, *J* = 2.6), 1.68 (m, 1 H), 1.95 (m, 1 H), 2.83 (s, 3 H), 3.17 (d, 1 H, *J* = 9.8), 3.94 (dd, 1 H, *J* = 2, 9.8), 4.27 (s, 1 H), 4.45 (m, 1 H), 5 (d, 1 H, *J* = 6.7), 6.95–7.55 (m, 18 H).

(2*R*,3*S*,4*S*)-2-(*N*-(9-Phenylfluoren-9-yl)-*N*-methylamino)-3-hydroxy-4-methyl-6-octynoic Acid (*R*)-α-Methylbenzylamide (D-(*R*)-38): ^1H NMR δ 0.93 (d, 3 H, *J* = 7), 0.94 (d, 3 H, *J* = 6.8), 1.18 (m, 1 H), 1.42 (t, 3 H, *J* = 2.5), 1.7 (m, 1 H), 1.95 (m, 1 H), 2.85 (s, 3 H), 3.25 (d, 1 H, *J* = 10), 3.83 (dd, 1 H, *J* = 1.6, 9.9), 4.25 (s, 1 H), 4.39 (m, 1 H), 4.95 (d, 1 H, *J* = 6.7), 7–7.6 (m, 18 H).

L-(*R*)-43: ^1H NMR δ 0.93 (d, 3 H, *J* = 6.7), 1.21 (s, 3 H), 1.29 (s, 3 H), 1.35 (m, 1 H), 1.5 (d, 3 H, *J* = 6.9), 1.6 (d, 3 H, *J* = 5), 1.7 (m, 2 H), 2.31 (s, 3 H), 3.14 (d, 1 H, *J* = 7.3), 3.65 (t, 1 H, *J* = 7), 5.1 (m, 1 H), 5.36 (m, 2 H), 7.2–7.4 (m, 5 H), 7.42 (br d, 1 H, *J* = 8.4).

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Registry No. L-**1**, 59865-23-5; D-**1**, 81177-28-8; **2**, 122213-51-8; **3**, 126459-24-3; **4**, 126459-25-4; **5**, 122213-53-0; **6**, 126459-26-5; **7**, 126459-27-6; **7** (R = $CH_2CH_2CH_3$), 126459-57-2; **8**, 126459-28-7; **9**, 126459-29-8; (4*S*)-**10**, 126459-30-1; (4*R*)-**10**, 126459-61-8; **11**, 126459-31-2; **12**, 126459-32-3; **13**, 126459-33-4; (*E*)-**14**, 126459-34-5; (*Z*)-**14**, 126459-58-3; (2′*R*)-**15**, 126459-35-6; (2′*S*)-**15**, 126459-59-4; **16**, 51703-97-0; (2′*R*)-**17**, 126459-36-7; (2′*S*)-**17**, 126459-60-7; (4*S*,1′*S*,2′*S*)-**19**, 126459-37-8; (4*S*,1′*S*,2′*R*)-**19**, 126576-03-2; (4*R*,1′*R*,2′*R*)-**19**, 126576-04-3; (4*R*,1′*R*,2′*S*)-**19**, 126576-05-4; **20**, 126459-38-9; **21**, 126459-39-0; **22**, 126459-40-3; **23**, 126459-41-4; **24**, 126459-42-5; **25**, 126459-43-6; **27**, 126459-44-7; **28**, 126459-45-8; **29**, 126459-46-9; **30**, 126459-47-0; **32**, 126501-62-0; **33**, 126459-48-1; (4*R*,5*S*,1′*S*)-**34**, 126459-49-2; (4*S*,5*R*,1′*R*)-**34**, 126459-62-9; **36**, 126459-50-5; (2*R*,3*S*,4*S*)-**37**, 126459-51-6; (2*S*,3*R*,4*R*)-**37**, 126576-06-5; L-(*R*)-**38**, 126459-52-7; D-(*R*)-**38**, 126637-91-0; (2*R*,3*S*,4*S*,6*Z*)-**39**, 126459-53-8; (2*S*,3*R*,4*R*,6*Z*)-**39**, 126576-07-6; **40**, 126459-54-9; L-**42**, 81135-31-1; L-(*R*)-**43**, 126459-55-0; BuLi, 109-72-8; EtLi, 811-49-4; EtMgBr, 925-90-6; $CH_3C{\equiv}CCH_2CH_2MgBr$, 126459-56-1; (*E*)-$CH_3CH{=}CHCH_2CH_2MgBr$, 37586-56-4; *s*-BuLi, 598-30-1; *s*-BuMgBr, 922-66-7; $BrCH_2CH_2C{\equiv}CCH_3$, 18719-27-2; $HOCH_2CH_2C{\equiv}CCH_3$, 10229-10-4; (*E*)-$HOCH_2CH_2CH{=}CHCH_3$, 764-37-4; (*E*)-$BrCH_2CH_2CH{=}CHCH_3$, 7515-62-0; Me_2CO, 67-64-1; (*R*)-(+)-PhCH(Me)NH_2, 3886-69-9; (±)-PhCH(Me)NH_2, 618-36-0; cyclosporin, 79217-60-0.

Tilifodiolide, Tetraline-Type Diterpenoid of Clerodanic Origin from *Salvia tiliaefolia*†

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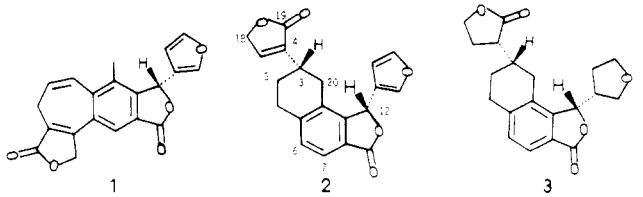
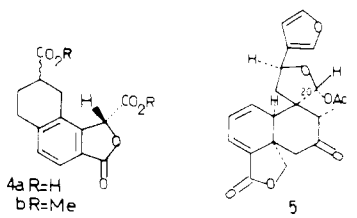
From the aerial parts of *Salvia tiliaefolia* Vahl, the known isosalvipuberulin (**1**) and two new clerodane diterpenoids, salvifolin and tilifodiolide, were isolated. The structure of salvifolin (**5**) was deduced from spectral data. The structure of tilifodiolide (**2**) was established by chemical and spectral means and X-ray diffraction analysis.

The *Salvia* spp. of Mexico and Central and South America have been classified in the Calosphace subgenus subdivided in 91 sections.[1] Systematic chemotaxonomic study of the Mexican *Salvia* species revealed an interesting relationship between the diterpenoid content of the species under study and the section to which it belongs.[2] There are however, some deviations from this generalization. Recently we described the structure elucidation of two new diterpenoids isolated from *Salvia puberula*,[3] which was classified in the Section Holwaya (Ramamoorthy)[4] closely related to Section Fulgentes.

In this paper we describe the diterpenoid constituents of *Salvia tiliaefolia* Vahl, a species classified[1] in Section Angulatae, Subsection Tiliaefoliae, which is not botanically related to Section Fulgentes. From the polar fraction of the acetone extract of *Salvia tiliaefolia*, we isolated the known isosalvipuberulin (**1**), previously obtained from



1 **2** **3**



4a R=H
b R=Me

5

Table I. ^1H NMR (400 MHz) and ^{13}C NMR (75 MHz) Data of Compound **2** ($CDCl_3$, TMS as Internal Standard)

C	^{13}C[a]	^1H δ[b]
1	29.2 t	3.01 ax, eq m
2	26.6 t	2.18 eq m; 1.76 ax, dddd (6, 9, 12, 13)
3	30.8 d	2.79 br t (12)
4	137.2 s	
5	143.8 d	6.95 dt (2, 1.5)
6	130.9 d	7.3 d (8)
7	123.0 d	7.7 d (8)
8	123.7 s	
9	130.5 s	
10	143.2 s	
11	147.2 s	
12	74.3 d	6.33 s
13	120.9 s	
14	142.1 d	7.52 t (1)
15	144.2 d	7.37 t (2)
16	108.7 d	6.08 dd (2, 1)
17	170.3 s	
18	173.3 s	
19	70.2 t	4.75 t (1.5)
20	30.4 t	2.90 eq, dd (4, 16); 2.21 ax, dd (1, 2, 16)

[a] SFORD multiplicities (at 20 MHz). [b] ax = pseudo-axial; eq = pseudo-equatorial, established by coupling patterns and NOE data.

Salvia puberula,[3] and a new diterpenoid named tilifodiolide, whose structure **2** was established by chemical and

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(1) Epling, C. *Rep. Spec. Nov. Beil.* **1939**, *110*, 1.
(2) (a) Rodríguez-Hahn, L.; Esquivel, B.; Sánchez, A.; Sánchez, C.; Cárdenas, J.; Ramamoorthy, T. P. *Rev. Latinoam. Quim.* **1987**, *18*, 104. (b) Rodríguez-Hahn, L.; Esquivel, B.; Sánchez, A.; Sánchez, C.; Cárdenas, J.; Ramamoorthy, T. P. *Rev. Latinoam. Quim.*, in press.
(3) The name puberulin has been previously used for a coumarin isolated from *Agathosma puberula* (*Phytochemistry* **1976**, *15*, 1080. Professor Rivett and Dr. S. A. Brown, personal communication); for this reason, we propose to name the diterpenoid described as "puberulin" (*J. Org. Chem.* **1988**, *53*, 3933) as *Salvipuberulin*.

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