JOURNAL OF combinatorial CHEMISTRY

Subscriber access provided by American Chemical Society

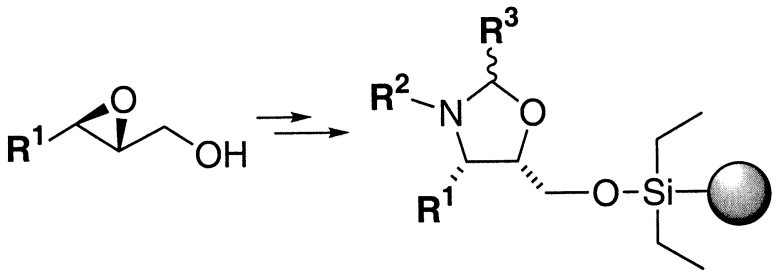
Article

Parallel Solid-Phase Synthesis and Structural Characterization of a Library of Highly Substituted Chiral 1,3-Oxazolidines

Martin R. Tremblay, Paul Wentworth,, George E. Lee,, and Kim D. Janda

J. Comb. Chem., **2000**, 2 (6), 698-709• DOI: 10.1021/cc0000500 • Publication Date (Web): 12 October 2000

Downloaded from http://pubs.acs.org on March 20, 2009



More About This Article

Additional resources and features associated with this article are available within the HTML version:

- Supporting Information
- Links to the 1 articles that cite this article, as of the time of this article download
- Access to high resolution figures
- Links to articles and content related to this article
- Copyright permission to reproduce figures and/or text from this article

View the Full Text HTML

ACS Publications
High quality. High impact.

Journal of Combinatorial Chemistry is published by the American Chemical Society.
1155 Sixteenth Street N.W., Washington, DC 20036

Parallel Solid-Phase Synthesis and Structural Characterization of a Library of Highly Substituted Chiral 1,3-Oxazolidines

Martin R. Tremblay, Paul Wentworth, Jr.,* George E. Lee, Jr.,† and Kim D. Janda*

Department of Chemistry and The Skaggs Institute for Chemical Biology, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, California 92037

Received June 14, 2000

The rapid parallel synthesis and characterization of diverse chirally defined 1,3-oxazolidines is reported. Three diversity elements were incorporated in a 6 × 4 × 4 block approach to generate a 96-member 1,3-oxazolidine library. The synthetic route involved initial attachment of six nonracemic phenylglycidols, (2*S*,3*S*)-**1A-C** and (2*R*,3*R*)-**2A-C**, to 2% cross-linked polystyrene resin via a chlorodiethylsilane linker (PS-DES), followed by regio- and stereoselective oxirane ring opening with four primary amines (**3a-d**). The key condensation reaction between the resulting polymer-bound β-amino alcohols and four aldehydes (**4a-d**) was found to occur optimally in warm benzene (60 °C) in the presence of anhydrous magnesium sulfate. Cleavage of the oxazolidines from the resin support was achieved with TBAF to give the individual members (2*R*,4*R*,5*R*)-**5Aaa-Cdd** and (2*S*,4*S*,5*S*)-**6Aaa-Cdd** in good to excellent yields (51−99%) based on mass recovery. Purities of all these crude products was generally >85% (as measured by LCMS). ^{1}H, ^{13}C NMR, and 1D difference nOe of the library members confirmed the structural and stereochemical integrity of the substituents around the 1,3-oxazolidine core. The asymmetric induction at C-2 (*cis* or *trans* to the C-4 substituent) ratio ranged from 4 to 1 to 49 to 1 across the library. This report highlights the versatility of the 1,3-oxazolidine heterocycle as a scaffold for concise parallel library construction and opens the way for high-throughput screening of such compounds in the biological sphere.

Introduction

Initial combinatorial strategies, driven by both existing solid-phase methodology and known pharmacophoric structures, focused on oligomeric materials such as peptides,[1−3] nucleotides,[4] and oligosaccharides.[5] However, the poor pharmacokinetic profile of such oligomeric materials has meant that most of today's therapeutic agents are small molecules, and therefore present combinatorial efforts are evolving toward libraries of such derivatives.[6,7] An approach receiving increasing interest is molecular scaffolding, whereby the synthesis of libraries of compounds occurs on multiply substituted templates that can be selectively and sequentially functionalized. Early templates included purine and triazine structures,[8−10] monosaccharides,[11−13] and polycarboxylic acids.[14,15] In this paper we describe the 1,3-oxazolidine heterocycle as a new scaffold for library synthesis.

1,3-Oxazolidines are remarkably versatile molecules having found use as chiral auxiliaries,[16,17] as intermediates for more complex chiral heterocycles,[18−22] and as prodrugs for improving the pharmacokinetic profile of certain β-amino alcohol pharmacophores.[23] They are ideally suited as scaffolds for combinatorial library generation because they have a rigid core that possesses four sites for the incorporation of diversity elements and can be synthesized with a high degree of chiral integrity (Figure 1A). We are exploring a systematic approach to the concise synthesis and characterization of chiral oxazolidine-based libraries, using nonracemic starting materials. Reported herein are our initial studies of the synthesis and characterization of chiral 1,3-oxazolidine libraries substituted at C-2, N-3, and C-4 (Figure 1B).

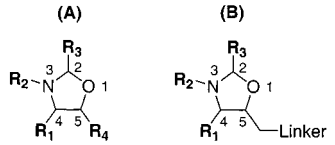


Figure 1. (A) 1,3-Oxazolidine heterocycle showing the four sites available for diversification. (B) Our initial 1,3-oxazolidine library motif with three points of diversity $\mathbf{R_1}-\mathbf{R_3}$ at C-4, N-3, and C-2, respectively, and a linker appendage at C-5.

Results and Discussion

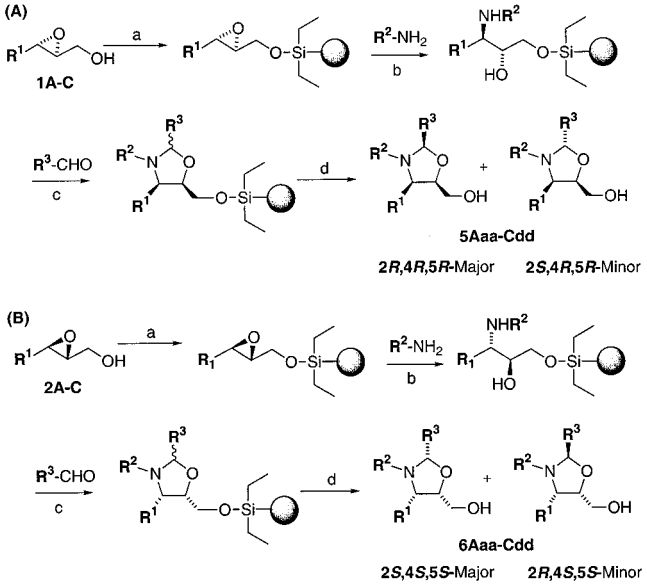
Library Design. The condensation of aldehydes with stereochemically defined β-amino alcohols under acidic conditions gives rise to oxazolidines where the *cis*-relationship between substituents at C-2 and C-4 predominates.[17,24−27] This stereoselectivity arises from thermodynamic control imposed during ring closure that involves a rapid equilibrium via an open-chain iminium ion.[28−30] We sought to exploit this known asymmetric induction at C-2 by coupling it with homochiral β-amino alcohol precursors such that the assembled 1,3-oxazolidines libraries possess high levels of diastereomeric purity. The general synthetic approach is shown in Scheme 1.

* Corresponding authors. P.W.: telephone (858) 784-2476; fax (858) 784-2590; e-mail paulw@scripps.edu. K.D.J.: telephone (858) 784-2515; fax: (858) 784-2595; e-mail kdjanda@scripps.edu.

† Structural and Physical Chemistry Dept., Aventis Research Center, Bridgewater, NJ.

10.1021/cc0000500 CCC: $19.00 © 2000 American Chemical Society
Published on Web 10/12/2000

Scheme 1. (A) Synthetic Route to the (2*R*,4*R*,5*R*)-Oxazolidine Library **5Aaa-Cdd** and (B) Synthetic Route to the (2*S*,4*S*,5*S*)-Oxazolidine Library **6Aaa-Cdd**[a]



[a] Reagents and conditions: (a) PS-DES resin (1.58 mmol/g), 1,3-dichloro-5,5-dimethylhydandtoin (3 equiv), phenylglycidol **1A-C** or **2A-C** (3 equiv), imidazole (4 equiv), CH_2Cl_2, rt, 4 h; (b) resin-supported oxiranes (0.2−0.4 mmol), ethanol:amine (**3a-d**) (1:1) (2 mL), sealed tube, 70 °C, 48 h; (c) resin-supported β-amino alcohols, aldehyde (**4a-d**) (25 equiv), benzene, $MgSO_4$, sealed tube, 60 °C; (d) resin-supported 1,3-oxazolidines, TBAF (1 M in THF, 3 equiv), THF, rt, 4 h.

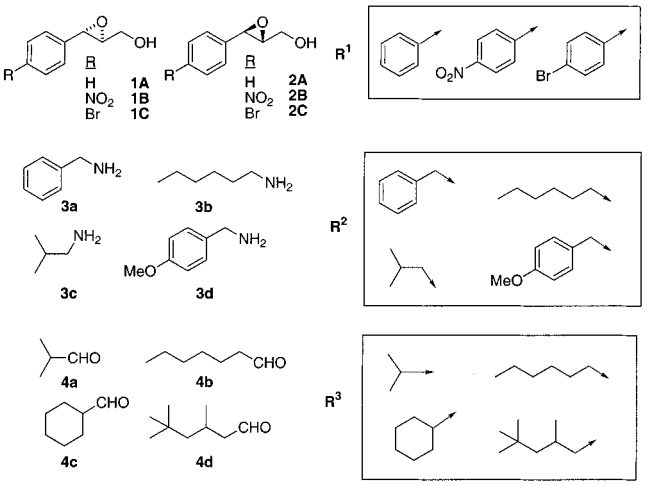


Figure 2. Diversity elements $\mathbf{R^1}$, $\mathbf{R^2}$, and $\mathbf{R^3}$ incorporated into the 1,3-oxazolidine library **5Aaa-Cdd** and **6Aaa-Cdd** by means of a 6 × 4 × 4 block strategy. Substituted phenylglycidols **1A-C** and **2A-C**, primary amines **3a-d**, and aldehydes **4a-d**.

The first stage in library construction involved the utilization of nonracemic substituted *trans* 3-phenylglycidol derivatives (2*S*,3*S*)-**1A-C** and (2*R*,3*R*)-**2A-C** that incorporate both the first diversity element $\mathbf{R^1}$ and a locus for attachment to the resin support (Figure 2). Regio- and stereoselective ring opening of these derivatives[31] is the key to establishing the chirality at C-4 (and hence C-2) and C-5 of the final oxazolidine library members. Furthermore, by exploiting enantiomeric epoxide antipodes (2*S*,3*S*)-**1A-C** and (2*R*,3*R*)-**2A-C** as starting points for the synthesis, the diversity of a racemic mixture is coupled to the benefits of having enantiomerically pure final compounds.

Nonracemic phenylglycidols are available either commercially or via Sharpless epoxidation[32] of the corresponding allylic alcohols. Initially we considered performing the Sharpless epoxidation on a resin-supported allylic alcohol. However, it has been reported that this reaction does not transfer well to heterogeneous conditions.[33] Therefore, in the cases where the phenylglycidol could not be obtained commercially, the chiral epoxidation was performed routinely in solution.

Selection of the amine and aldehyde building blocks, for incorporation of the $\mathbf{R^2}$ and $\mathbf{R^3}$ diversity elements, respectively, required optimization studies. The regio- and stereoselective opening of the glycidols (protected as their TBDMS ethers) in solution was shown to be a general reaction that was successful using either unbranched or branched aliphatic primary amines, benzylic amines, as well as anilines by utilizing Crotti's method.[34] As predicted,[31] the primary amines attack the oxiranes at the benzylic carbon, as determined by ^{13}C NMR and ^1H NMR spectroscopy, to generate β-amino alcohols with almost complete regioselectivity (see Experimental Section).

The condensation reaction between the β-amino alcohols and aldehydes to form 1,3-oxazolidines is acid-catalyzed; therefore, a number of conditions were explored, including solvent (EtOH, benzene, toluene, $CHCl_3$, CH_2Cl_2), acids (PPTS, *p*-TSA, CH_3SO_2H), dehydrating agents ($MgSO_4$, 4 Å molecular sieves), and temperature (25 °C and reflux). The mildest conditions applicable for the condensation reaction were found to be anhydrous $MgSO_4$ in benzene at 60 °C.

The optimization studies also refined the amines and aldehydes that could be incorporated into the library. Aromatic aldehydes were found to be unsuitable building blocks because they require particularly harsh condensation conditions (longer reaction times and higher temperatures) that concomitantly lead to product and starting material decomposition. In addition, anilines were discarded because the ring closure proceeds in both low yields and with poor discrimination of the two diastereoisomers at C-2. Therefore, it was ascertained that the ideal combination of building blocks was comprised of unbranched, branched aliphatic, or benzylic amines (**3a-d**) coupled with branched or unbranched aliphatic aldehydes (**4a-d**) (Figure 2).

The next challenge was to establish a suitable linker strategy. Two important aspects were taken into consideration. While phenylglycidol **2A** has previously been coupled to halo-substituted resins via the use of NaH with no evidence of chiral scrambling,[35] a concern that glycidols **1B-C** and **2B-C** (R = NO_2 or Br) may be unstable to strong bases, being susceptible to the Payne rearrangement,[36] meant that such conditions were avoided during attachment to the polymer. Furthermore, 1,3-oxazolidines are sensitive to acidic conditions, thus precluding the selection of acid-labile linkers such as Wang, Barlos,[37] or Ellman's[38] which would be problematic during the cleavage step. Therefore we selected 2% cross-linked polystyrene derivatized with chlorodiethylsilane as the polymer support (PS-DES),[39] rationalizing that cleavage with TBAF would be a suitably mild and orthogonal method.

Table 1. Characterization of the (2*R*,4*R*,5*R*)-1,3-Oxazolidine Library **5Aaa-Cdd**

entry	R_1	R_2	R_3	yield[a]/%	purity[b]/%	ratio[c] 2*R*:2*S*
5Aaa	H	benzyl	isopropyl	92	>98	80:20
5Aab	H	benzyl	hexyl	69	95	>90:10
5Aac	H	benzyl	cyclohexyl	59	>98	83:17
5Aad	H	benzyl	2,2,4-$(Me)_3$-pentyl	67	68	ND
5Aba	H	hexyl	isopropyl	64	>98	92:8
5Abb	H	hexyl	hexyl	82	87	96:4
5Abc	H	hexyl	cyclohexyl	68	>98	92:8
5Abd	H	hexyl	2,2,4-$(Me)_3$-pentyl	59	54	ND
5Aca	H	isobutyl	isopropyl	81	>98	84:16
5Acb	H	isobutyl	hexyl	70	>98	>95:5
5Acc	H	isobutyl	cyclohexyl	65	>98	83:17
5Acd	H	isobutyl	2,2,4-$(Me)_3$-pentyl	59	84	ND
5Ada	H	4-MeO-benzyl	isopropyl	70	>98	81:19
5Adb	H	4-MeO-benzyl	hexyl	70	>98	89:11
5Adc	H	4-MeO-benzyl	cyclohexyl	60	>98	82:18
5Add	H	4-MeO-benzyl	2,2,4-$(Me)_3$-pentyl	50	54	ND
5Baa	NO_2	benzyl	isopropyl	82	>98	94:6
5Bab	NO_2	benzyl	hexyl	77	>98	>98:2
5Bac	NO_2	benzyl	cyclohexyl	79	>98	87:13
5Bad	NO_2	benzyl	2,2,4-$(Me)_3$-pentyl	85	>98	>95:5
5Bba	NO_2	hexyl	isopropyl	97	>98	84:16
5Bbb	NO_2	hexyl	hexyl	89	>98	94:6
5Bbc	NO_2	hexyl	cyclohexyl	72	>98	97:3
5Bbd	NO_2	hexyl	2,2,4-$(Me)_3$-pentyl	83	>98	88:12
5Bca	NO_2	isobutyl	isopropyl	84	>98	83:17
5Bcb	NO_2	isobutyl	hexyl	85	>98	>98:2
5Bcc	NO_2	isobutyl	cyclohexyl	92	>98	87:13
5Bcd	NO_2	isobutyl	2,2,4-$(Me)_3$-pentyl	63	>98	>95:5
5Bda	NO_2	4-MeO-benzyl	isopropyl	63	>98	94:6
5Bdb	NO_2	4-MeO-benzyl	hexyl	65	>98	96:4
5Bdc	NO_2	4-MeO-benzyl	cyclohexyl	92	>98	94:6
5Bdd	NO_2	4-MeO-benzyl	2,2,4-$(Me)_3$-pentyl	64	81	>95:5
5Caa	Br	benzyl	isopropyl	55	>98	79:21
5Cab	Br	benzyl	hexyl	99	95	>95:5
5Cac	Br	benzyl	cyclohexyl	71	>98	85:15
5Cad	Br	benzyl	2,2,4-$(Me)_3$-pentyl	94	88	99:1
5Cba	Br	hexyl	isopropyl	68	>98	>98:2
5Cbb	Br	hexyl	hexyl	94	>98	96:4
5Cbc	Br	hexyl	cyclohexyl	87	>98	89:11
5Cbd	Br	hexyl	2,2,4-$(Me)_3$-pentyl	91	91	ND
5Cca	Br	isobutyl	isopropyl	84	>98	89:11
5Ccb	Br	isobutyl	hexyl	95	>98	>98:2
5Ccc	Br	isobutyl	cyclohexyl	99	87	78:22
5Ccd	Br	isobutyl	2,2,4-$(Me)_3$-pentyl	99	>98	ND
5Cda	Br	4-MeO-benzyl	isopropyl	94	>98	81:19
5Cdb	Br	4-MeO-benzyl	hexyl	92	>98	94:6
5Cdc	Br	4-MeO-benzyl	cyclohexyl	80	>98	86:14
5Cdd	Br	4-MeO-benzyl	2,2,4-$(Me)_3$-pentyl	89	80	ND

[a] Based on mass recovery of the crude product after cleavage from the PS-DES resin. [b] Determined by LCMS. [c] Determined by ^{1}H NMR.

Library Synthesis. Parallel solid-phase synthesis of the 1,3-oxazolidine libraries was initiated by the coupling of each enantiomer of the *trans* 3-phenylglycidol derivatives (2*S*,3*S*)-**1A-C** and (2*R*,3*R*)-**2A-C** onto the PS-DES resin in its chlorinated form (Scheme 1).[39] The direct attachment of (2*S*,3*S*)-**1A-C** and (2*R*,3*R*)-**2A-C** can also be achieved via Wilkinson's catalyst mediated alcoholysis of the polymer-bound trialkylsilane.[40] However, the purities of the final oxazolidine compounds (isolated after cleavage from the resin) were higher using the former procedure. The derivatization of the PS-DES resin with the oxirane was monitored by gel-phase ^{13}C NMR according to the procedure described by Lorgé and co-workers[41] and typically proceeded in up to 97% completion.

The regio- and stereoselective opening of these polymer-bound oxiranes was then performed in parallel by heating the resin-supported glycidols at 70 °C in the presence of the amines (**3a-d**) in ethanol. Subsequent condensation of the polymer-bound β-amino alcohols with aliphatic aldehydes (**4a-d**) using $MgSO_4$ in benzene (60 °C) led to the 1,3-oxazolidines, confirmed by the presence of the characteristic signal of C-2 at ca. 99 ppm in the gel-phase ^{13}C NMR spectrum.

The cleavage of the PS-DES-supported 1,3-oxazolidines was performed with TBAF in THF at room temperature. Although the reaction with pyridine-HF complex was also successful, the lability of some library members toward acidic aqueous medium prompted the choice of the fluoride-mediated cleavage for the whole library. At this stage all the library members (**5Aaa-Cdd** and **6Aaa-Cdd**) were characterized in their crude forms by ^{1}H NMR and by liquid-chromatography coupled to a mass spectrometer (LCMS).

Table 2. Characterization of the (2*S*,4*S*,5*S*)-1,3-Oxazolidine Library **6Aaa-Cdd**

entry	R_1	R_2	R_3	yield[a]/%	purity[b]/%	ratio[c] 2*S*:2*R*
6Aaa	H	benzyl	isopropyl	51	>98	85:15
6Aab	H	benzyl	hexyl	64	95	>9:1
6Aac	H	benzyl	cyclohexyl	55	>98	84:16
6Aad	H	benzyl	2,2,4-$(Me)_3$-pentyl	55	91	>95:5
6Aba	H	hexyl	isopropyl	55	>98	>95:5
6Abb	H	hexyl	hexyl	59	90	94:6
6Abc	H	hexyl	cyclohexyl	64	>98	94:6
6Abd	H	hexyl	2,2,4-$(Me)_3$-pentyl	51	29	ND
6Aca	H	isobutyl	isopropyl	71	>98	91:9
6Acb	H	isobutyl	hexyl	65	>98	92:8
6Acc	H	isobutyl	cyclohexyl	69	>98	89:11
6Acd	H	isobutyl	2,2,4-$(Me)_3$-pentyl	69	>85	ND
6Ada	H	4-MeO-benzyl	isopropyl	62	>98	81:19
6Adb	H	4-MeO-benzyl	hexyl	54	>98	95:5
6Adc	H	4-MeO-benzyl	cyclohexyl	73	>98	83:17
6Add	H	4-MeO-benzyl	2,2,4-$(Me)_3$-pentyl	61	>90	>95:5
6Baa	NO_2	benzyl	isopropyl	66	>98	9:1
6Bab	NO_2	benzyl	hexyl	78	>98	96:4
6Bac	NO_2	benzyl	cyclohexyl	70	>98	9:1
6Bad	NO_2	benzyl	2,2,4-$(Me)_3$-pentyl	65	>98	93:7
6Bba	NO_2	hexyl	isopropyl	75	>98	9:1
6Bbb	NO_2	hexyl	hexyl	97	>95	98:2
6Bbc	NO_2	hexyl	cyclohexyl	63	>98	96:4
6Bbd	NO_2	hexyl	2,2,4-$(Me)_3$-pentyl	74	>95	98:2
6Bca	NO_2	isobutyl	isopropyl	74	>98	79:11
6Bcb	NO_2	isobutyl	hexyl	82	>98	>98:2
6Bcc	NO_2	isobutyl	cyclohexyl	72	>98	84:16
6Bcd	NO_2	isobutyl	2,2,4-$(Me)_3$-pentyl	87	>98	98:2
6Bda	NO_2	4-MeO-benzyl	isopropyl	74	81	92:8
6Bdb	NO_2	4-MeO-benzyl	hexyl	79	94	95:5
6Bdc	NO_2	4-MeO-benzyl	cyclohexyl	74	93	9:1
6Bdd	NO_2	4-MeO-benzyl	2,2,4-$(Me)_3$-pentyl	72	>90	>95:5
6Caa	Br	benzyl	isopropyl	70	>98	78:22
6Cab	Br	benzyl	hexyl	74	>95	93:7
6Cac	Br	benzyl	cyclohexyl	75	>98	84:16
6Cad	Br	benzyl	2,2,4-$(Me)_3$-pentyl	90	>98	ND
6Cba	Br	hexyl	isopropyl	94	>95	91:9
6Cbb	Br	hexyl	hexyl	80	>95	95:5
6Cbc	Br	hexyl	cyclohexyl	76	>98	89:11
6Cbd	Br	hexyl	2,2,4-$(Me)_3$-pentyl	77	>90	ND
6Cca	Br	isobutyl	isopropyl	67	>98	87:13
6Ccb	Br	isobutyl	hexyl	81	>98	94:6
6Ccc	Br	isobutyl	cyclohexyl	74	>98	86:14
6Ccd	Br	isobutyl	2,2,4-$(Me)_3$-pentyl	78	>98	98:2
6Cda	Br	4-MeO-benzyl	isopropyl	71	>98	84:16
6Cdb	Br	4-MeO-benzyl	hexyl	90	>98	94:6
6Cdc	Br	4-MeO-benzyl	cyclohexyl	75	>98	82:18
6Cdd	Br	4-MeO-benzyl	2,2,4-$(Me)_3$-pentyl	78	>98	ND

[a] Based on mass recovery of the crude product after cleavage from the PS-DES resin. [b] Determined by LCMS. [c] Determined by ^{1}H NMR.

In addition, the **5Aaa-Cdd** sub-library was also characterized by ^{13}C NMR.

This facile and concise route generates the 1,3-oxazolidines in good yield—(2*R*,4*R* 5*R*)-**5Aaa-Cdd** 50−99% (mean yield 78%); (2*S*,4*S*,5*S*)-**6Aaa-Cdd** 51−97% (mean yield 71.4%)—and excellent purity following the cleavage step (determined by ^{1}H, ^{13}C NMR, and LCMS) (see Tables 1 and 2).

The branched aldehyde **4d** was the only building block that caused any problems during library construction, reflected in purities of <85% for some of its oxazolidine derivatives (**5Aad**, **5Abd**, **5Acd**, **5Add**, **5Bdd**, **5Cdd**, and **6Abd**). Although the source of the poor yield has not been thoroughly investigated, it may be a result of either insufficient time for the condensation reaction or increased sensitivity to the TBAF cleavage reaction.

Library Analysis. There were a number of issues that needed resolving once the completed library was in hand, all of which were related to the structural integrity of the individual library members. First, how regio- and stereoselective was the aminolysis of the polymer-supported glycidol derivatives, especially because no reagents were utilized to assist the regioselective ring-opening process. Second, what is the relative proportion of the *cis* C-2 and C-4 relationship vide supra. To help answer these questions, samples of each member of the library were analyzed by a combination of NMR techniques, establishing the relative stereochemistry of the subsituents at C-2, C-4, and C-5 around the oxazolidine ring.

Interestingly, the presence of any oxazolidine resulting from the ring closure of the minor regioisomer of the β-amino

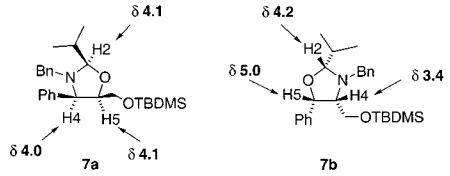


Figure 3. ^{1}H NMR assignments for the ring protons of 1,3-oxazolidines derived from regioisomeric β-amino alcohol precursors.

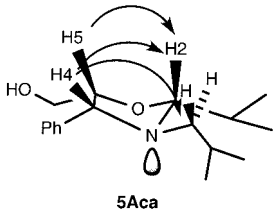


Figure 4. Relative stereochemistry assignment based on nOe contacts (highlighted by arrows) betweeen H-2, H-4, H-5, and the benzylic protons attached to N-3 for the 1,3-oxazolidine **5Aca**.

alcohols (generated from incomplete regioselectivity during aminolysis of the glycidols) was barely detectable by ^{1}H NMR (less than 2%). A model 1,3-oxazolidine **7b**, derived from this minor regioisomer, was prepared (synthesized using an L-serine derivative as the starting material), and the ^{1}H NMR assignments for the ring protons H-2, H-4, and H-5 were compared with those of the major isomer **7a** (synthesized in solution via Crotti's[34] regioselective aminolysis procedure). This allowed the key issue of regioselectivity in the aminolysis reaction to be established unambiguously (Figure 3).

For example, the H-4 signal typically appears at 4.0 ppm when the nitrogen is attached to the benzylic position (as with **7a**) while the corresponding chemical shift of H-5 is 5.0 ppm for oxazolidine **7b** (which bears the oxygen at that position). The difference between the chemical shift of the H-5 proton is also large (ca. 0.5 ppm), but is not as useful a probe because of the presence of other signals that may appear in this region. The difference between the H-2 signals of the regioisomers is marginal (ca. 0.1 ppm) and therefore is not definitive. These data were also supported by existing literature describing related 1,3-oxazolidine compounds.[28,30]

Inspection of the ^{1}H NMR spectra of all the crude library members (**5Aaa-Cdd** and **6Aaa-Cdd**) reveals a small signal at 5.0−5.2 ppm, corresponding to the benzylic proton of the minor regioisomer of the oxazolidine (H-5). Therefore, it can be stated that the opening of the polymer-bound epoxides with primary amines **3a-d** was indeed highly regioselective for the benzylic position.[28,30]

Although amine-mediated oxirane opening is expected to proceed via an S_N2-mechanism, the benzylic group may stabilize the carbocation generated by the S_N1 route, leading to stereochemical scrambling at the benzylic carbon (C-3) of the resultant β-amino alcohols. Thus, we closely looked at the possible presence of stereoisomers at the C-4 benzylic position within the oxazolidine library. The dihedral angle between H-4 and H-5 on the oxazolidine ring should be around 15° for the proposed *cis*-4,5 substitution, whereas it would be approximatively 110° for the corresponding epimer at the position 4 (*trans*-4,5). The observed coupling constant displayed between H-4 and H-5 throughout the library members is consistently 8 Hz, and therefore, according to the Karplus correlation, the most likely configuration of our library corresponds to the protons on C-4 and C-5 having a *cis* relationship. Our data are also in agreement with NMR data for closely related 1,3-oxazolidin-2-ones where it was found that the coupling constants were larger for the *cis* than the *trans* system.[42,43] Our observations also support the notion that the polymer-supported epoxide ring opening was both regio- and stereoselective, and that the final oxazolidine libraries are chirally defined, as required. This then allows not only an assignment of the relative stereochemistry of each library, but the absolute stereochemistry based on the known enantioselectivity of the Sharpless epoxidation reaction.

Comparison of the ^{1}H NMR spectra of the crude oxazolidine products with existing literature data indicated that the ratio of the two corresponding diastereoisomers at the C-2 position varied from 4:1 to 49:1, always in favor of the most thermodynamically stable all-*cis* isomer.[26] A notable difference is observed between the chemical shifts of the H-2 protons of the isomeric species, the one situated *syn* to the nitrogen lone pair being the more deshielded and hence downfield (ca. 0.5 ppm). Additional information about the configuration of the substituents around the five-member ring was also obtained by 1D difference nuclear Overhausser enhancement (nOe) experiments. We chose the oxazolidine **5Aca** as the model compound because it contains a significant proportion (15%) of what was considered to be its C-2 epimer based on 1D ^{1}H NMR analysis (Figure 4). This gave us an ideal opportunity to simultaneously investigate the relative environment of the ring protons of these two diastereomers under identical conditions. For the major component **5Aca**, a strong nOe signal was observed between H-4 and H-5, again supporting the 4,5-*cis* relationship vide supra. Moreover, an nOe contact was also found between H-4 and H-2, confirming an all-*cis* structure for **5Aca**. For the minor diastereoisomer *epi*-**5Aca**, the 4,5-*cis* relationship was also confirmed by an nOe contact between H-4 and H-5. However, no nOe was observed between either H-4 and H-2 or H-5 and H-2. These data support the fact that *epi*-**5Aca** is the corresponding C-2 epimer and validate our initial assignment. Finally, there is a significant nOe contact between H-4 and the methylene protons attached to N-3. This supports the previously observed phenomenon that substituents at N-3 adopt an equatorial geometry *trans* to the *cis* C-2 and C-4 substituents.[25,26,30,44] Consequently, each library member is constituted of mainly one diastereoisomer (the *cis*-2,4), together with a small amount of the other diastereoisomer (*trans*-2,4), with the substituent on N-3 adopting a *trans*-relative geometry to the substituents on C-2 and C-4. The presence of any other isomers of these oxazolidines (as a result of the incomplete regio- and stereoselectivity of the epoxide aminolysis reaction) is not significant.

Conclusion

We have described a concise and stereocontrolled method for the solid-phase synthesis of a highly functionalized and chirally defined 96-member library of 1,3-oxazolidines. This

process involves facile parallel chemistry that leads to molecules in excellent yield and purity. Three centers of molecular diversity have been identified: the substituted phenyl ring at C-4, the substituent on the N-3 nitrogen, and the alkyl group at C-2. These molecules are at present undergoing screening for biological activity.

Experimental Section

General Methods. Reagents were obtained from Sigma-Aldrich Co. (Milwaukee, WI). PS-DES resin was purchased at Argonaut Technologies (Santa Carlos, CA). (2*S*,3*S*)-*trans*-3-Phenyloxirane-2-methanol **1A** and (2*R*,3*R*)-*trans*-3-phenyloxirane-2-methanol **2A** were purchased from Fluka. (2*S*,3*S*)-(−)-3-(4-nitrophenyl)glycidol **1B** and (2*R*,3*R*)-(+)-3-(4-nitrophenyl)glycidol **2B** were provided by Aldrich Chemical Co. (Milwaukee, WI). Usual solvents were obtained from Fisher and were used as received. Anhydrous dimethylformamide (DMF), benzene, and toluene, were obtained from Aldrich in SureSeal bottles, which were conserved under positive argon pressure. Tetrahydrofuran (THF) was distilled from sodium/benzophenone ketyl under argon. Methylene chloride was continuously distilled from calcium hydride. Unless otherwise stated, reactions were carried out in flame-dried glassware under an atmosphere of argon. Reagents and solvents were transferred with plastic syringes and oven-dried needles. Large scale solid-phase reactions were performed in peptide-flasks fritted glass tubes equipped for vacuum filtration (ChemGlass Inc., Vineland, NJ) and were agitated with a Ika-Vibrax-Vxr shaker (Germany). Small scale parallel solid-phase reactions were performed using a Syro Manual System (MultiSyntech, Germany). Flash chromatographies were performed on E. Merck 60 230−400 mesh silica gel. Thin-layer chromatographies were performed on 0.25 mm E. Merck silica gel 60 F_{254} plates and visualized by UV (254 nm) and/or cerium ammonium molybdate. Infrared (IR) spectra were recorded on a Pelkin-Elmer series 1600 FT-IR spectrometer, and the significant bands were reported in cm^{-1} only. Nuclear magnetic resonance (NMR) spectra were recorded either at 500 or 400 MHz for ^1H and at the respective frequencies for ^{13}C on a Bruker AMX-500 or AMX-400 instrument. LC/MS were performed using a Micromass LCT mass spectrometer operating in electrospray ionization mode with a resolution of 5000. The sample solution was infused into the mass spectrometer at 100 μL/min in a water/acetonitrile/formic acid mobile phase under a 4 min gradient. The sample cone voltage was maintained at 40 V and gave approximately the same molecular ion intensities.

Asymmetric Epoxidation. (2*S*,3*S*)-(−)-3-(Bromophenyl)-glycidol **1C** and (2*R*,3*R*)-(+)-3-(4-bromophenyl)glycidol **2C** were prepared by the procedure described by Sharpless et al.[45] All the spectroscopic data and optical rotations were in agreement with the literature values. **1C**: Lit.[45] $[\alpha]^{25}_D$: −35.2° (c = 2, $CHCl_3$); obtained: −34.1° (c = 2, $CHCl_3$). **2C**: Lit.[45] $[\alpha]^{25}_D$: +35.2° (c = 2, $CHCl_3$); obtained: +33.5° (c = 2, $CHCl_3$).

Solution-Phase Optimization Studies. 1. Amine-Mediated Oxirane Opening.[34] Benzylamine (74 μL; 0.68 mmol) was syringed into a mixture of (2*S*,3*S*)-*trans*-3-phenyl-2-[(*tert*-butyldimethylsilyl)oxy]oxirane (36 mg; 0.14 mmol) and $LiClO_4$ (660 mg; 6 mmol) in 1 mL of dry CH_3CN at 55 °C under argon. The mixture was allowed to stir at this temperature for 2 h and cooled to room temperature. Water was added, and the aqueous layer was extracted with diethyl ether. The combined organic extracts were dried over Na_2SO_4 and evaporated to dryness. The crude oil was passed through a small silica gel pad eluting with hexane:EtOAc (8:2) to give 44 mg (87%) of a colorless oil. Both ^1H and ^{13}C NMR data were in agreement with the exclusive addition at the C-3 position.[46] The other regioisomer of this β-amino alcohol was synthesized in a straightforward manner from an advanced intermediate described in the literature.[47]

2. Typical Condensation of β-Amino Alcohol with Aldehyde in Solution. A solution of (2*R*,3*R*)-3-phenyl-2-benzylamino-propan-(*tert*-butyldimethylsilyl)oxy]-ol (18 mg; 0.048 mmol) in dry benzene (500 μL) was stirred in the presence of isobutyraldehyde (44 μL; 0.48 mmol) and anhydrous $MgSO_4$ (30 mg) for 3 h at 60 °C. The mixture was filtered through Celite, and the filtrate was concentrated under reduced pressure. The crude oil was purified by semiprep TLC (0.5 mm) eluting with hexane:EtOAc:Et_3N (85:14:1) to give 12 mg (59%) of the desired oxazolidine. The other regioisomer of this oxazolidine was obtained using the same procedure on the corresponding β-amino alcohol regioisomer (see Figure 3).

Library Synthesis. Attachment of the Glycidols [(2*S*,3*S*)-1A-C and (2*R*,3*R*)-2A-C)] to the PS-DES Resin.[39] In a dry peptide-flask under argon, PS-DES resin (1.2 g; 1.58 mmol/g) was treated with a solution of freshly recrystallized 1,3-dichloro-5,5-dimethylhydantoin (1.1 g; 5.7 mmol) in 10 mL of anhydrous CH_2Cl_2. The reaction mixture was vortexed for 1.5 h, and the resin was filtered and then washed with dry CH_2Cl_2 (3 × 10 mL) and THF (3 × 10 mL) under argon. After a short period under vacuum (15 min), the resin was treated immediately with a solution of the substituted phenyloxiranemethanol (2*S*,3*S*)-**1A-C** and (2*R*,3*R*)-**2A-C** (5.7 mmol) and imidazole (450 mg; 6.6 mmol) in 10 mL of dry CH_2Cl_2. The resulting slurry was allowed to vortex for 4 h at 25 °C. The mixture was then filtered, and the resin was washed with DMF (3 × 5 mL), DMF:H_2O (1:1) (3 × 5 mL), THF:H_2O (1:1) (3 × 5 mL), and THF (3 × 5 mL). The resin was dried under vacuum until the weight was judged constant (18 h), i.e., 1.48 g (97%, based on weight increase).

Solid-Phase Aminolysis of PS-Supported Epoxides. The phenyloxiranemethanol derivatives resins (310 to 330 mg; 0.2 to 0.4 mmol) were placed individually in 16 × 100 Pyrex screw cap tubes (Science Products) equipped with small magnetic stir-bars (1.5 × 8 mm) and treated with 2 mL of a mixture of absolute EtOH:amine (**3a-d**) (1:1). The tubes were placed in the Syro Multisyntech manual synthesizer and stirred at intervals (30 s/stir and 30 s/pause) at 70 °C. After 48 h, the resulting resins were filtered using a polypropylene (PP)-syringe equipped with polyethylene (PE)-fritts and washed with DMF (3 × 3 mL), CH_2Cl_2 (3 × 3 mL), and MeOH (3 × 3 mL). The resins were then dried under vacuum overnight.

Solid-Phase Condensation of PS-Supported β-Amino Alcohols with Aldehydes (4a-d). The β-amino alcohol resins (~75 mg; 0.075 mmol) were placed individually in 16 × 100 Pyrex scew cap tubes (Science Products) equipped with small magnetic stir-bars (1.5 × 8 mm) and swollen in dry benzene (1 mL). Aldehydes (**4a-d**) (200 μL, ~25 equiv) and anhydrous $MgSO_4$ (50−60 mg) were added to each corresponding tube, which were stirred at intervals (30 s/stir and 30 s/pause) at 60 °C in the Multisyntech reaction block. After 24 h, the resulting resins were filtered using a PP-syringe equipped with PE-fritts and washed with DMF (3 × 2 mL), DMF:H_2O (1:1) (3 × 2 mL), H_2O (3 × 2 mL), THF (3 × 2 mL), and MeOH (3 × 2 mL). The resins were then dried under vacuum overnight.

Cleavage of the 1,3-Oxazolidine Library from the PS-DES Support. Each resin (45−65 mg) was cleaved separately as follows. The beads were swollen with THF (700 μL) and treated with 1 M tetrabutylammonium fluoride in THF (150 μL). The resulting mixtures were vortexed using a Vibrax shaker for 4 h at 25 °C. The mixture was filtered, and the resin was washed once with THF (1 mL) and twice with diethyl ether (1 mL). The filtrate was then washed with saturated aqueous $NaHCO_3$ solution (3 mL). The aqueous phase was frozen in a 14 mL polypropylene round-bottom tube (Falcon, 352059) using an EtOH/dry ice bath, and the organic phase was decanted. The aqueous phase was then re-extracted with ether (2 mL). The combined organic layers were washed successively with H_2O and brine using the freezing/decanting procedure vide supra. Evaporation of the organic solvent under a nitrogen stream followed by drying under vacuum overnight yielded the individual oxazolidine library members (**5Aaa-Cdd** and **6Aaa-Cdd**) (typically 15−20 mg of the desired products were obtained as oils).

5Aaa: ^{1}H NMR ($CDCl_3$): 1.00 and 1.01 (2d, J = 7.3 Hz, 6H, 2 × CH_3), 1.90 (m, 1H, C*H*(CH_3)$_2$), 3.06 (dd, J_1 = 11.4 Hz and J_2 = 4.4 Hz, 1H, 1H of CH_2O), 3.34 (dd, J_1 = 11.4 Hz and J_2 = 8.0 Hz, 1H, 1H of CH_2O), 3.56 and 3.85 (2d, J = 14.3 Hz, 2H, NCH_2Ph), 4.03 (d, J = 8.1 Hz, 1H, H4), 4.16 (d, J = 1.8 Hz, 1H, H2), 4.17 (m, 1H, H5), 7.0−7.5 (m, 10 H, Ar). ^{13}C NMR ($CDCl_3$): 14.5, 19.1, 29.6, 54.1, 63.4, 68.2, 78.4, 99.0, 127.1, 127.8 128.0 (2C), 128.1 (2C), 128.2 (2C), 129.3(2C), 129.5, 136.8. MS: Calcd for $C_{20}H_{26}NO_2$ $[M + H]^+$: 312.2. Found: 312.2. Purity LCMS: >98% (rt: 2.06 min).

5Aab: ^{1}H NMR ($CDCl_3$): 0.89 (t, J = 7.1 Hz, 3H, CH_3), 1.0−1.6 (m, 10H, CH_2 of hexyl), 3.11 (dd, J_1 = 11.6 Hz and J_2 = 4.4 Hz, 1H, 1H of CH_2O), 3.31 (dd, J_1 = 11.6 Hz and J_2 = 7.2 Hz, 1H, 1H of CH_2O), 3.53 and 3.89 (2d, J = 14.1 Hz, 2H, NCH_2Ph), 4.02 (d, J = 7.9 Hz, 1H, H4), 4.18 (td, J_1 = 7.8 Hz, J_2 = 7.2 Hz, J_3 = 4.4 Hz, 1H, H5), 4.27 (dd, J_1 = 7.1 Hz and J_2 = 2.1 Hz, 1H, H2), 7.1−7.4 (m, 10 H, Ar). ^{13}C NMR ($CDCl_3$): 14.1, 22.6, 24.0, 29.3, 31.8, 34.1, 54.3, 63.4, 68.6, 79.0, 95.8, 127.1, 127.8, 128.0 (2C), 128.2 (2C), 128.5 (2C), 129.2 (3C), 137.0. MS: Calcd for $C_{23}H_{32}NO_2$ $[M + H]^+$: 354.3. Found: 354.3. Purity LCMS: 95% (rt: 2.25 min).

5Aac: ^{1}H NMR ($CDCl_3$): 0.97 (m, 2H, 4-CH_2 of cyclohexyl), 1.0−1.9 (m, 8H, CH_2 of cyclohexyl), 1.95 (m, 1H, CH of cyclohexyl), 3.06 (dd, J_1 = 11.6 Hz and J_2 = 4.4 Hz, 1H, 1H of CH_2O), 3.31 (dd, J_1 = 11.6 Hz and J_2 = 7.7 Hz, 1H, 1H of CH_2O), 3.52 and 3.87 (2d, J = 14.0 Hz, 2H, NCH_2Ph), 3.99 (d, J = 8.1 Hz, 1H, H4), 4.12 (d, J = 4.4 Hz, 1H, H2), 4.16 (td, J_1 = 8.1 Hz, J_2 = 7.7 Hz, J_3 = 4.4 Hz, 1H, H5), 7.0−7.4 (m, 10 H, Ar). ^{13}C NMR ($CDCl_3$): 25.3, 26.0, 26.7, 26.9, 29.8, 40.0, 54.4, 63.3, 68.3, 78.6, 99.0, 127.1, 127.7, 128.0 (2C), 128.1 (2C), 128.2 (2C), 129.2 (2C), 129.5, 137.0. MS: Calcd for $C_{23}H_{30}NO_2$ $[M + H]^+$: 352.2. Found: 352.3. Purity LCMS: >98% (rt: 2.26 min).

5Aba: ^{1}H NMR ($CDCl_3$): 0.80 (t, J = 7.1 Hz, 3H, CH_3 of hexyl), 1.0−1.3 (m, 14H, CH_2 of hexyl and CH_3 of isopropyl), 1.90 (m, 1H, C*H*(CH_3)$_2$), 2.50 (m, 2H, CH_2N), 3.04 (dd, J_1 = 11.6 Hz and J_2 = 4.4 Hz, 1H, 1H of CH_2O), 3.25 (dd, J_1 = 11.4 Hz and J_2 = 7.7 Hz, 1H, 1H of CH_2O), 3.97 (d, J = 8.3 Hz, 1H, H4), 4.09 (d, J = 2.6 Hz, 1H, H2), 4.20 (td, J_1 = 8.3 Hz, J_2 = 7.7 Hz, J_3 = 4.4 Hz, 1H, H5), 7.1−7.4 (m, 5H, Ar). ^{13}C NMR ($CDCl_3$): 14.0, 14.9, 19.2, 22.5, 27.2, 27.8, 30.7, 31.5, 51.6, 63.4, 69.6, 79.1, 99.6, 127.5, 128.1 (2C), 128.2 (2C), 138.9. MS: Calcd for $C_{19}H_{32}NO_2$ $[M + H]^+$: 306.2. Found: 306.3. Purity LCMS: >98% (rt: 1.80 min).

5Abb: ^{1}H NMR ($CDCl_3$): 0.81 (t, J = 7.0 Hz, 3H, CH_3 of hexyl), 0.91 (t, J = 7.0 Hz, 3H, CH_3 of hexyl), 1.0−1.8 (m, 18H, CH_2 of hexyl), 2.52 (m, 2H, CH_2N), 3.10 (dd, J_1 = 11.7 Hz and J_2 = 4.4 Hz, 1H, 1H of CH_2O), 3.21 (dd, J_1 = 11.7 Hz and J_2 = 7.3 Hz, 1H, 1H of CH_2O), 3.93 (d, J = 7.7 Hz, 1H, H4), 4.20 (m, 2H, H5 and H2), 7.2−7.4 (m, 5H, Ar). ^{13}C NMR ($CDCl_3$): 14.0, 14.1, 22.5, 22.7, 24.5, 27.1, 28.1, 29.5, 31.5, 31.9, 34.8, 51.7, 63.3, 69.4, 79.7, 96.3, 127.5, 128.0 (2C), 128.2 (2C), 139.1. MS: Calcd for $C_{22}H_{38}NO_2$ $[M + H]^+$: 348.3. Found: 348.3. Purity LCMS: 87% (rt: 1.88 min).

5Abc: ^{1}H NMR ($CDCl_3$): 0.80 (m, 5H, CH_3 of hexyl and 4-CH_2 of cyclohexyl), 1.0−1.9 (m, 16H, CH_2 of hexyl and CH_2 of cyclohexyl), 2.05 (m, 1H, CH of cyclohexyl), 2.50 (m, 2H, CH_2N), 3.06 (dd, J_1 = 11.6 Hz and J_2 = 4.4 Hz, 1H, 1H of CH_2O), 3.22 (dd, J_1 = 11.7 Hz and J_2 = 7.7 Hz, 1H, 1H of CH_2O), 3.94 (d, J = 8.3 Hz, 1H, H4), 4.05 (d, J = 2.8 Hz, 1H, H2), 4.17 (td, J_1 = 8.3 Hz, J_2 = 7.7 Hz, J_3 = 4.4 Hz, 1H, H5), 7.3−7.4 (m, 5H, Ar). ^{13}C NMR ($CDCl_3$): 14.0, 22.5, 25.7, 26.2, 26.8, 26.9, 27.1, 27.8, 29.9, 31.5, 41.0, 51.7, 63.4, 69.4, 79.3, 99.4, 127.5, 128.1 (2C), 128.1 (2C), 139.1. MS: Calcd for $C_{22}H_{36}NO_2$ $[M + H]^+$: 346.3. Found: 346.3. Purity LCMS: >98% (rt: 1.99 min).

5Aca: ^{1}H NMR ($CDCl_3$): 0.71 and 0.76 (2d, J = 6.6 and 6.2 Hz, 6H, 2 × CH_3 of isobutyl), 1.08 and 1.11 (2d, J = 6.8 Hz, 6H, 2 × CH_3 of isopropyl), 1.43 (m, 1H, C*H*(CH_3)$_2$), 1.94 (m, 1H, C*H*(CH_3)$_2$), 2.23 (dd, J_1 = 12.5 Hz and J_2 = 9.1 Hz, 1H, 1H of CH_2N), 2.35 (dd, J_1 = 12.5 Hz and J_2 = 5.9 Hz, 1H, 1H of CH_2N), 3.07 (dd, J_1 = 11.5 Hz and J_2 = 4.4 Hz, 1H, 1H of CH_2O), 3.24 (dd, J_1 = 11.5 Hz and J_2 = 7.9 Hz, 1H, 1H of CH_2O), 3.83 (d, J = 8.1 Hz, 1H, H4), 4.00 (d, J = 2.8 Hz, 1H, H2), 4.20 (td, J_1 = 8.1 Hz, J_2 = 7.9 Hz, J_3 = 4.4 Hz, 1H, H5), 7.3−7.5 (m, 5H, Ar);^{13}C NMR ($CDCl_3$): 15.3, 19.4, 20.2, 20.8, 21.2, 27.5, 31.0, 62.5, 63.3, 71.2, 79.51, 100.8, 127.4, 128.2 (2C), 129.3, 139.8. MS: Calcd for $C_{17}H_{28}NO_2$ $[M + H]^+$: 278.2. Found: 278.2. Purity LCMS: >98% (rt: 1.98 min).

5Acb: ^{1}H NMR ($CDCl_3$): 0.71 and 0.79 (2d, J = 6.6 and 6.2 Hz, 6H, 2 × CH_3 of isobutyl), 0.91 (m, 3H, CH_3 of hexyl), 1.0−1.6 (m, 10H, CH_2 of hexyl), 1.75 (m, 1H, C*H*$(CH_3)_2$), 2.22 (dd, J_1 = 12.5 Hz and J_2 = 9.1 Hz, 1H, 1H of CH_2N), 2.38 (dd, J_1 = 12.5 Hz and J_2 = 5.9 Hz, 1H, 1H of CH_2N), 3.13 (dd, J_1 = 11.5 Hz and J_2 = 4.4 Hz, 1H, 1H of CH_2O), 3.21 (dd, J_1 = 11.5 Hz and J_2 = 7.9 Hz, 1H, 1H of CH_2O), 3.83 (d, J = 7.7 Hz, 1H, H4), 4.13 (d, J = 2.2 Hz, 1H, H2), 4.19 (m, 1H, H5), 7.3−7.5 (m, 5H, Ar). ^{13}C NMR ($CDCl_3$): 14.1, 20.8, 22.5, 24.8, 27.6, 28.8, 29.6, 31.9, 35.1, 62.0, 63.2, 70.8, 80.0, 97.2, 127.4, 128.0 (2C), 128.1 (2C), 139.75. MS: Calcd for $C_{20}H_{34}NO_2$ [M + H]$^+$: 320.3. Found: 320.3. Purity LCMS: >98% (rt: 2.13 min).

5Acc: ^{1}H NMR ($CDCl_3$): 0.71 and 0.76 (2d, J = 6.6 and 6.2 Hz, 6H, 2 × CH_3 of isobutyl), 1.0−1.9 (m, 11H, CH_2 of cyclohexyl and C*H*$(CH_3)_2$), 2.13 (m, 1H, CH of cyclohexyl), 2.24 (dd, J_1 = 12.5 Hz and J_2 = 9.1 Hz, 1H, 1H of CH_2N), 2.36 (dd, J_1 = 12.5 Hz and J_2 = 5.9 Hz, 1H, 1H of CH_2N), 3.07 (dd, J_1 = 11.6 Hz and J_2 = 4.1 Hz, 1H, 1H of CH_2O), 3.23 (dd, J_1 = 11.7 Hz and J_2 = 7.7 Hz, 1H, 1H of CH_2O), 3.81 (d, J = 8.1 Hz, 1H, H4), 3.98 (d, J = 2.9 Hz, H2), 4.18 (td, J_1 = 8.1 Hz, J_2 = 7.7 Hz, J_3 = 4.4 Hz, 1H, H5), 7.3−7.5 (m, 5H, Ar). ^{13}C NMR ($CDCl_3$): 20.8, 21.2, 26.0, 26.3, 26.7, 26.8, 27.6, 30.0, 41.2, 62.6, 63.3, 71.0, 79.6, 100.5, 127.4, 128.0 (2C), 128.1 (2C), 140.0. MS: Calcd for $C_{20}H_{32}NO_2$ [M + H]$^+$: 318.2. Found: 318.3. Purity LCMS: >98% (rt: 2.18 min).

5Ada: ^{1}H NMR ($CDCl_3$): 0.95 and 1.01 (2d, J = 6.8 Hz, 6H, 2 × CH_3 of isopropyl), 1.75 (m, 1H, C*H*$(CH_3)_2$), 3.05 (dd, J_1 = 11.7 Hz and J_2 = 4.4 Hz, 1H, 1H of CH_2O), 3.33 (dd, J_1 = 11.7 Hz and J_2 = 7.7 Hz, 1H, 1H of CH_2O), 3.51 (d, J = 14.3 Hz, 1H, 1H of $ArCH_2N$), 3.78 (m, 4H, CH_3O and 1H of $ArCH_2N$), 4.01 (d, J = 8.1 Hz, 1H, H4), 4.14 (m, 2H, H5 and H2), 6.76 (d, J = 8.4 Hz, 2H, 2 × CH of Ar), 7.02 (d, J = 8.4 Hz, 2H, 2 × CH of Ar), 7.35 (m, 5H, Ar). ^{13}C NMR ($CDCl_3$): 14.4, 19.1, 29.5, 53.0, 55.2, 63.4, 67.9, 78.4, 98.6, 113.4 (2C), 127.7, 128.3 (2C), 128.5 (2C), 128.6, 130.4 (2C), 136.8, 158.7. MS: Calcd for $C_{21}H_{28}NO_3$ [M + H]$^+$: 342.2. Found: 342.2. Purity LCMS: >98% (rt: 1.92 min).

5Adb: ^{1}H NMR ($CDCl_3$): 0.88 (t, J = 7.0 Hz, 3H, CH_3 of hexyl), 1.0−1.7 (m, 10H, CH_2 of hexyl), 3.10 (dd, J_1 = 11.4 Hz and J_2 = 4.4 Hz, 1H, 1H of CH_2O), 3.30 (dd, J_1 = 11.7 Hz and J_2 = 7.0 Hz, 1H, 1H of CH_2O), 3.49 (d, J = 14.1 Hz, 1H, 1H of $ArCH_2N$), 3.81 (m, 4H, CH_3O and 1H of $ArCH_2N$), 4.01 (d, J = 7.6 Hz, 1H, H4), 4.15 (ABX system, 1H, H5), 4.25 (dd, J_1 = 6.0 Hz and J_2 = 2.0 Hz, 1H, H2), 6.78 (d, J = 8.6 Hz, 2H, 2 × CH of Ar), 7.04 (d, J = 8.6 Hz, 2H, 2 × CH of Ar), 7.3−7.4 (m, 5H, Ar). ^{13}C NMR ($CDCl_3$): 14.1, 22.6, 24.0, 29.3, 31.8, 34.0, 53.1, 55.2, 63.4, 68.1, 78.9, 95.3, 113.4 (2C), 127.7, 128.2 (2C), 128.5 (2C), 128.8, 130.4 (2C), 137.0, 158.7. MS: Calcd for $C_{24}H_{34}NO_3$ [M + H]$^+$: 384.3. Found: 384.3. Purity LCMS: >98% (rt: 2.02 min).

5Adc: ^{1}H NMR ($CDCl_3$): 1.00 (m, 2H, 4-CH_2 of cyclohexyl), 1.1−1.8 (m, 8H, CH_2 of cyclohexyl), 1.96 (m, 1H, CH of cyclohexyl), 3.04 (dd, J_1 = 11.4 Hz and J_2 = 4.4 Hz, 1H, 1H of CH_2O), 3.32 (dd, J_1 = 11.4 Hz and J_2 = 7.7 Hz, 1H, 1H of CH_2O), 3.50 (d, J = 13.9 Hz, 1H, 1H of $ArCH_2N$), 3.80 (m, 4H, CH_3O and 1H of $ArCH_2N$), 3.97 (d, J = 7.6 Hz, 1H, H4), 4.11 (m, 2H, H5 and H2), 6.77 (d, J = 8.4 Hz, 2H, 2 × CH of Ar), 7.03 (d, J = 8.4 Hz, 2H, 2 × CH of Ar), 7.3−7.4 (m, 5H, Ar). ^{13}C NMR ($CDCl_3$): 25.3, 26.1, 26.7, 26.9, 29.8, 39.9, 53.2, 55.3, 63.4, 67.8, 78.6, 98.5, 113.4 (2C), 127.7, 128.2 (2C), 128.4 (2C), 128.7 (2C), 129.4, 130.4 (2C), 137.0, 158.8. MS: Calcd for $C_{24}H_{32}NO_3$ [M + H]$^+$: 382.2. Found: 382.3. Purity LCMS: >98% (rt: 2.12 min).

5Baa: ^{1}H NMR ($CDCl_3$): 1.07 and 1.08 (2d, J = 6.9 Hz, 6H, 2 × CH_3), 1.90 (m, 1H, C*H*$(CH_3)_2$), 3.02 (dd, J_1 = 11.6 Hz and J_2 = 4.0 Hz, 1H, 1H of CH_2O), 3.23 (dd, J_1 = 11.6 Hz and J_2 = 7.5 Hz, 1H, 1H of CH_2O), 3.68 and 3.77 (2d, J = 13.8 Hz, 2H, NCH_2Ph), 4.07 (d, J = 8.2 Hz, 1H, H4), 4.21 (d, J = 2.7 Hz, 1H, H2), 4.23 (ABX system, 1H, H5), 7.0−7.3 (m, 5H, Ar), 7.42 (d, J = 8.8 Hz, 2H, 2 × CH_2 of $ArNO_2$), 8.06 (d, J = 8.8 Hz, 2H, 2 × CH_2 of $ArNO_2$). ^{13}C NMR ($CDCl_3$): 14.5, 19.1, 30.0, 55.4, 62.9, 68.1, 78.9, 99.2, 123.2 (2C), 127.4, 128.1 (2C), 128.3 (2C), 129.2 (2C), 136.5, 146.4, 147.2. MS: Calcd for $C_{20}H_{25}N_2O_4$ [M + H]$^+$: 357.2. Found: 357.2. Purity LCMS: >98% (rt: 2.10 min).

5Bab: ^{1}H NMR ($CDCl_3$): 0.88 (m, 3H, CH_3 of hexyl), 1.1−1.8 (m, 10H, CH_2 of hexyl), 3.07 (dd, J_1 = 11.6 Hz and J_2 = 4.0 Hz, 1H, 1H of CH_2O), 3.20 (dd, J_1 = 11.7 Hz and J_2 = 7.3 Hz, 1H, 1H of CH_2O), 3.73 (s, 2H, $PhCH_2N$), 4.06 (d, J = 8.1 Hz, 1H, H4), 4.25 (ABX system, 1H, H5), 4.35 (dd, J_1 = 6.6 Hz and J_2 = 2.2 Hz, 1H, H2), 7.0−7.2 (m, 5H, Ar), 7.44 (d, J = 8.6 Hz, 2H, 2 × CH_2 of $ArNO_2$), 8.08 (d, J = 8.6 Hz, 2H, 2 × CH_2 of $ArNO_2$). ^{13}C NMR ($CDCl_3$): 14.1, 22.6, 24.3, 29.3, 31.8, 34.0, 55.4, 62.8, 68.0, 79.3, 96.0, 123.2 (2C), 127.4, 128.1 (3C), 129.0 (3C), 136.8, 146.5, 147.2. MS: Calcd for $C_{23}H_{31}N_2O_4$ [M + H]$^+$: 399.2. Found: 399.3. Purity LCMS: >98% (rt: 2.35 min).

5Bac: ^{1}H NMR ($CDCl_3$): 0.92 (m, 2H, 4-CH_2 of cyclohexyl), 1.1−1.9 (m, 8H, CH_2 of cyclohexyl), 2.05 (m, 1H, CH of cyclohexyl), 3.02 (dd, J_1 = 11.5 Hz and J_2 = 4.0 Hz, 1H, 1H of CH_2O), 3.22 (dd, J_1 = 11.6 Hz and J_2 = 7.6 Hz, 1H, 1H of CH_2O), 3.70 and 3.75 (2d, J = 13.6 Hz, 2H, $PhCH_2N$), 4.03 (d, J = 8.1 Hz, 1H, H4), 4.19 (d, J = 2.6 Hz, 1H, H2), 4.23 (td, J_1 = 8.0 Hz, J_2 = 7.6 Hz, J_3 = 4.0 Hz, 1H, H5), 7.0−7.2 (m, 5H, Ar), 7.42 (d, J = 8.8 Hz, 2H, 2 × CH of $ArNO_2$), 8.08 (d, J = 8.8 Hz, 2H, 2 × CH of $ArNO_2$). ^{13}C NMR ($CDCl_3$): 25.8, 26.0, 26.6, 26.7, 29.8, 40.3, 55.7, 62.8, 68.0, 79.0, 99.2, 123.2 (2C), 127.4, 128.0 (2C), 128.2 (2C), 129.1 (2C), 136.7, 146.6, 147.2. MS: Calcd for $C_{23}H_{29}N_2O_4$ [M + H]$^+$: 397.2. Found: 397.2. Purity LCMS: >98% (rt: 2.27 min).

5Bba: ^{1}H NMR ($CDCl_3$): 0.78 (t, J = 6.8 Hz, 3H, CH_3 of hexyl), 1.0−1.5 (m, 14H, CH_2 of hexyl and 2 × CH_3 of isopropyl), 1.96 (m, 1H, C*H*$(CH_3)_2$), 2.55 (2m, 2H, CH_2N), 3.05 (dd, J_1 = 11.6 Hz and J_2 = 4.0 Hz, 1H, 1H of CH_2O), 3.16 (dd, J_1 = 11.4 Hz and J_2 = 7.6 Hz, 1H, 1H of CH_2O), 4.03 (d, J = 8.5 Hz, 1H, H4), 4.09 (d, J = 2.9 Hz, 1H, H2), 4.25 (td, J_1 = 8.0 Hz, J_2 = 7.6 Hz, J_3 = 4.0 Hz, 1H, H5), 7.56 (d, J = 8.8 Hz, 2H, 2 × CH of $ArNO_2$), 8.16 (d, J = 8.8 Hz, 2H, 2 × CH of $ArNO_2$). ^{13}C NMR ($CDCl_3$): 13.9, 15.2, 19.1, 22.5, 27.0, 28.4, 30.7, 31.4, 52.3, 62.9, 69.0, 79.2, 99.7, 123.3 (2C), 128.9 (2C), 147.3, 148.2. MS: Calcd for $C_{19}H_{31}N_2O_4$ [M + H]$^+$: 351.2. Found: 351.3. Purity LCMS: >98% (rt: 2.30 min).

5Bbb: ^{1}H NMR ($CDCl_3$): 0.79 (t, J = 7.0 Hz, 3H, CH_3 of hexyl), 0.91 (m, 3H, CH_3 of hexyl), 1.1−1.9 (m, 18H, CH_2 of both hexyl groups), 2.55 (m, 2H, CH_2N), 3.14 (ABX system, 2H, CH_2O), 3.99 (d, J = 8.0 Hz, 1H, H4), 4.23 (m, 2H, H5 and H2), 7.53 (d, J = 8.8 Hz, 2H, 2 × CH of $ArNO_2$), 8.15 (d, J = 8.8 Hz, 2H, 2 × CH of $ArNO_2$). ^{13}C NMR ($CDCl_3$): 13.9, 14.1, 22.4, 22.6, 24.6, 26.9, 28.6, 29.5, 31.4, 31.8, 34.4, 52.2, 62.8, 68.7, 79.8, 96.4, 123.2 (2C), 128.8 (2C), 147.3, 148.3. MS: Calcd for $C_{22}H_{37}N_2O_4$ $[M + H]^+$: 393.3. Found: 393.3. Purity LCMS: >98% (rt: 2.50 min).

5Bbc: ^{1}H NMR ($CDCl_3$): 0.79 (t, J = 7.0 Hz, 3H, CH_3 of hexyl), 1.0−1.9 (m, 18H, CH_2 of cyclohexyl), 2.05 (m, 1H, CH of cyclohexyl), 2.50 and 2.57 (2m, 2H, CH_2N), 3.06 (dd, J_1 = 11.6 Hz and J_2 = 4.0 Hz, 1H, 1H of CH_2O), 3.15 (dd, J_1 = 11.7 Hz and J_2 = 7.7 Hz, 1H, 1H of CH_2O), 3.99 (d, J = 8.1 Hz, 1H, H4), 4.05 (d, J = 2.9 Hz, 1H, H2), 4.23 (ABX system, 1H, H5), 7.55 (d, J = 8.8 Hz, 2H, 2 × CH of $ArNO_2$), 8.16 (d, J = 8.8 Hz, 2H, 2 × CH of $ArNO_2$). ^{13}C NMR ($CDCl_3$): 13.9, 22.5, 26.0, 26.1, 26.6, 26.7, 27.0, 28.4, 29.8, 31.4, 40.9, 52.4, 62.8, 68.9, 79.4, 99.5, 123.2 (2C), 128.9 (2C), 147.3, 148.4. MS: Calcd for $C_{22}H_{35}N_2O_4$ $[M + H]^+$: 391.3. Found: 391.3. Purity LCMS: >98% (rt: 2.50 min).

5Bca: ^{1}H NMR ($CDCl_3$): 0.68 and 0.76 (2d, J = 6.6 and 6.2 Hz, 6H, 2 × CH_3 of isobutyl), 1.09 and 1.12 (2d, J = 6.8 Hz, 6H, 2 × CH_3 of isopropyl), 1.37 (m, 1H, C*H*$(CH_3)_2$), 1.96 (m, 1H, C*H*$(CH_3)_2$), 2.28 (dd, J_1 = 12.5 Hz and J_2 = 9.9 Hz, 1H, 1H of CH_2N), 2.40 (dd, J_1 = 12.5 Hz and J_2 = 4.8 Hz, 1H, 1H of CH_2N), 3.08 (dd, J_1 = 11.5 Hz and J_2 = 4.0 Hz, 1H, 1H of CH_2O), 3.19 (dd, J_1 = 11.5 Hz and J_2 = 7.9 Hz, 1H, 1H of CH_2O), 3.91 (d, J = 8.1 Hz, 1H, H4), 4.00 (d, J = 3.3 Hz, 1H, H2), 4.25 (td, J_1 = 8.1 Hz, J_2 = 7.9 Hz, J_3 = 4.0 Hz, 1H, H5), 7.56 (d, J = 8.8 Hz, 2H, 2 × CH of $ArNO_2$), 8.15 (d, J = 8.8 Hz, 2H, 2 × CH of $ArNO_2$);^{13}C NMR ($CDCl_3$): 15.6, 19.3, 20.5, 21.1, 27.8, 31.0, 62.6 (2C), 70.4, 79.4, 100.7, 123.2 (2C), 128.8 (2C), 147.3, 148.7. MS: Calcd for $C_{17}H_{27}N_2O_4$ $[M + H]^+$: 323.2. Found: 323.2. Purity LCMS: >98% (rt: 2.13 min).

5Bcb: ^{1}H NMR ($CDCl_3$): 0.66 and 0.77 (2d, J = 6.6 and 6.2 Hz, 6H, 2 × CH_3 of isobutyl), 0.91 (m, 3H, CH_3 of hexyl), 1.2−1.8 (m, 11H, CH_2 of hexyl and C*H*$(CH_3)_2$), 2.26 (dd, J_1 = 12.5 Hz and J_2 = 9.5 Hz, 1H, 1H of CH_2N), 2.43 (dd, J_1 = 12.5 Hz and J_2 = 5.1 Hz, 1H, 1H of CH_2N), 3.12 (ABX system, 2H, CH_2O), 3.91 (d, J = 7.7 Hz, 1H, H4), 4.19 (dd, J_1 = 7.3 Hz and J_2 = 2.6 Hz, 1H, H2), 4.24 (td, J_1 = 7.8 Hz, J_2 = 7.7 Hz, J_3 = 4.4 Hz, 1H, H5), 7.53 (d, J = 8.8 Hz, 2H, 2 × CH of $ArNO_2$), 8.15 (d, J = 8.8 Hz, 2H, 2 × CH of $ArNO_2$). ^{13}C NMR ($CDCl_3$): 14.1, 20.5, 20.9, 22.6, 24.9, 27.8, 29.5, 31.9, 34.7, 62.1, 62.6, 69.9, 80.1, 97.1, 123.2 (2C), 128.8 (2C), 147.3, 148.7. MS: Calcd for $C_{20}H_{33}N_2O_4$ $[M + H]^+$: 365.2. Found: 365.2. Purity LCMS: >98% (rt: 2.44 min).

5Bcc: ^{1}H NMR ($CDCl_3$): 0.68 and 0.76 (2d, J = 6.8 and 6.6 Hz, 6H, 2 × CH_3 of isobutyl), 0.8−1.9 (m, 11H, CH_2 of cyclohexyl and C*H*$(CH_3)_2$), 2.05 (m, 1H, CH of cyclohexyl), 2.29 (dd, J_1 = 12.5 Hz and J_2 = 9.9 Hz, 1H, 1H of CH_2N), 2.40 (dd, J_1 = 12.5 Hz and J_2 = 5.0 Hz, 1H, 1H of CH_2N), 3.08 (dd, J_1 = 11.6 Hz and J_2 = 4.1 Hz, 1H, 1H of CH_2O), 3.16 (dd, J_1 = 11.6 Hz and J_2 = 7.7 Hz, 1H, 1H of CH_2O), 3.89 (d, J = 8.1 Hz, 1H, H4), 4.01 (d, J = 3.3 Hz, 1H, H2), 4.23 (td, J_1 = 8.0 Hz, J_2 = 7.7 Hz, J_3 = 4.1 Hz, 1H, H5), 7.55 (d, J = 8.8 Hz, 2H, 2 × CH of $ArNO_2$), 8.15 (d, J = 8.8 Hz, 2H, 2 × CH of $ArNO_2$). ^{13}C NMR ($CDCl_3$): 20.5, 21.1, 26.2, 26.3, 26.6, 26.7, 27.8, 29.9, 41.1, 62.7 (2C), 70.2, 79.7, 100.4, 123.2 (2C), 128.9 (2C), 147.3, 148.8. MS: Calcd for $C_{20}H_{31}N_2O_4$ $[M + H]^+$: 363.2. Found: 363.3. Purity LCMS: >98% (rt: 2.35 min).

5Bda: ^{1}H NMR ($CDCl_3$): 1.06 and 1.08 (2d, J = 7.0 and 6.6 Hz, 6H, 2 × CH_3 of isopropyl), 1.93 (m, 1H, C*H*$(CH_3)_2$), 3.01 (dd, J_1 = 11.6 Hz and J_2 = 4.0 Hz, 1H, 1H of CH_2O), 3.22 (dd, J_1 = 11.6 Hz and J_2 = 7.6 Hz, 1H, 1H of CH_2O), 3.66 and 3.77 (2d, J = 18 Hz, 2H, $ArCH_2N$), 3.72 (s, 3H, CH_3O), 4.05 (d, J = 8.4 Hz, 1H, H4), 4.22 (m, 2H, H5 and H2), 6.68 (d, J = 8.8 Hz, 2H, 2 × CH of ArOMe), 6.95 (d, J = 8.8 Hz, 2H, 2 × CH of ArOMe), 7.43 (d, J = 8.8 Hz, 2H, 2 × CH of $ArNO_2$), 8.09 (d, J = 8.8 Hz, 2H, 2 × CH of $ArNO_2$). ^{13}C NMR ($CDCl_3$): 14.9, 19.1, 29.9, 54.4, 55.2, 62.9, 67.7, 78.7, 99.0, 113.4 (2C), 123.2 (2C), 128.4, 129.2 (2C), 129.9 (2C), 146.4, 147.2, 158.9. MS: Calcd for $C_{21}H_{27}N_2O_5$ $[M + H]^+$: 387.2. Found: 387.2. Purity LCMS: >98% (rt: 2.05 min).

5Bdb: ^{1}H NMR ($CDCl_3$): 0.90 (t, J = 7.2 Hz, 3H, CH_3 of hexyl), 1.1−1.8 (m, 10H, CH_2 of hexyl), 3.06 (dd, J_1 = 11.6 Hz and J_2 = 4.0 Hz, 1H, 1H of CH_2O), 3.19 (dd, J_1 = 11.6 Hz and J_2 = 7.3 Hz, 1H, 1H of CH_2O), 3.73 (s, 3H, CH_3O), 3.78 (m, 2H, $ArCH_2N$), 4.05 (d, J = 8.1 Hz, 1H, H4), 4.23 (ABX system, 1H, H4), 4.33 (dd, J_1 = 6.4 Hz and J_2 = 2.2 Hz, 1H, H2), 6.69 (d, J = 8.5 Hz, 2H, 2 × CH of ArOMe), 6.97 (d, J = 8.5 Hz, 2H, 2 × CH of ArOMe), 7.44 (d, J = 8.7 Hz, 2H, 2 × CH of $ArNO_2$), 8.09 (d, J = 8.7 Hz, 2H, 2 × CH of $ArNO_2$). ^{13}C NMR ($CDCl_3$): 14.1, 22.6, 24.3, 29.4, 31.8, 33.9, 54.4, 55.2, 62.9, 67.7, 79.2, 95.7, 113.5 (2C), 123.2 (2C), 128.7, 129.0 (2C), 130.3 (2C), 146.5, 147.2, 158.9. MS: Calcd for $C_{24}H_{33}N_2O_5$ $[M + H]^+$: 429.2. Found: 429.3. Purity LCMS: >98% (rt: 2.29 min).

5Bdc: ^{1}H NMR ($CDCl_3$): 0.94 (m, 2H, 4-CH_2 of cyclohexyl), 1.0−1.9 (m, 8H, CH_2 of cyclohexyl), 2.05 (m, 1H, CH of cyclohexyl), 3.02 (dd, J_1 = 11.7 Hz and J_2 = 4.0 Hz, 1H, 1H of CH_2O), 3.21 (dd, J_1 = 11.7 Hz and J_2 = 7.7 Hz, 1H, 1H of CH_2O), 3.72 (s, 3H, CH_3O), 3.78 (m, 2H, $ArCH_2N$), 4.02 (d, J = 8.4 Hz, 1H, H4), 4.17 (d, J = 2.9 Hz, 1H, H2), 4.21 (td, J_1 = 8.2 Hz, J_2 = 7.8 Hz, J_3 = 4.0 Hz, 1H, H5), 6.67 (d, J = 8.6 Hz, 2H, 2 × CH of ArOMe), 6.95 (d, J = 8.6 Hz, 2H, 2 × CH of ArOMe), 7.42 (d, J = 8.6 Hz, 2H, 2 × CH of $ArNO_2$), 8.09 (d, J = 8.6 Hz, 2H, 2 × CH of $ArNO_2$). ^{13}C NMR ($CDCl_3$): 13.7, 20.3, 25.7, 26.1, 26.7, 29.7, 30.3, 40.2, 54.6, 55.2, 62.8, 67.6, 78.9, 98.9, 113.4 (2C), 123.1 (2C), 128.5, 129.0 (2C), 130.3 (2C), 146.6, 147.1, 158.9. MS: Calcd for $C_{24}H_{31}N_2O_5$ $[M + H]^+$: 427.2. Found: 427.2. Purity LCMS: >98% (rt: 2.25 min).

5Caa: ^{1}H NMR ($CDCl_3$): 0.98 and 1.02 (2d, J = 6.9 Hz, 6H, 2 × CH_3), 1.80 (m, 1H, C*H*$(CH_3)_2$), 3.03 (dd, J_1 = 11.7 Hz and J_2 = 4.4 Hz, 1H, 1H of CH_2O), 3.29 (dd, J_1 = 11.7 Hz and J_2 = 7.9 Hz, 1H, 1H of CH_2O), 3.61 and 3.77 (2d, J = 14 Hz, 2H, NCH_2Ph), 3.96 (d, J = 8.1 Hz, 1H, H4), 4.15 (m, 2H, H5 and H2), 7.08 (dd, J_1 = 7.0 Hz and J_2 = 2.4 Hz, 2H, 2 × CH of Ar), 7.21 (m, 5H, CH of Ar), 7.41

(d, J = 8.4 Hz, 2H, 2 × CH of Ar). ^{13}C NMR ($CDCl_3$): 14.6, 19.1, 29.7, 54.4, 63.2, 67.7, 78.4, 99.0, 121.4, 127.2, 128.2 (2C), 129.2 (2C), 130.0 (2C), 131.3 (2C), 136.6 (2C). MS: Calcd for $C_{20}H_{25}BrNO_2$ $[M + H]^+$: 390.1. Found: 390.1. Purity LCMS: >98% (rt: 2.24 min).

5Cab: ^{1}H NMR ($CDCl_3$): 0.88 (m, 3H, CH_3 of hexyl), 1.1−1.7 (m, 10H, CH_2 of hexyl), 3.09 (dd, J_1 = 11.7 Hz and J_2 = 4.0 Hz, 1H, 1H of CH_2O), 3.26 (dd, J_1 = 11.7 Hz and J_2 = 7.3 Hz, 1H, 1H of CH_2O), 3.58 and 3.81 (2d, J = 14 Hz, 2H, NCH_2Ph), 3.95 (d, J = 7.7 Hz, 1H, H4), 4.17 (td, J_1 = 7.7 Hz, J_2 = 7.7 Hz, J_3 = 4.0 Hz, 1H, H5), 4.28 (dd, J_1 = 6.6 Hz and J_2 = 2.2 Hz, 1H, H2), 7.12 (dd, J_1 = 7.0 Hz and J_2 = 2.2 Hz, 2H, 2 × CH of Ar), 7.22 (m, 5H, CH of Ar), 7.42 (d, J = 8.4 Hz, 2H, 2 × CH of Ar). ^{13}C NMR ($CDCl_3$): 14.1, 22.6, 24.1, 29.3, 31.8, 34.0, 54.5, 63.2, 67.9, 79.0, 95.7, 121.4, 127.2, 128.1 (2C), 129.1 (2C), 129.9 (2C), 131.4 (2C), 136.6, 136.9. MS: Calcd for $C_{23}H_{31}BrNO_2$ $[M + H]^+$: 432.2. Found: 390.1. Purity LCMS: 95% (rt: 2.48 min).

5Cac: ^{1}H NMR ($CDCl_3$): 0.93 (m, 2H, 4-CH_2 of cyclohexyl), 1.1−1.8 (m, 8H, CH_2 of cyclohexyl), 1.95 (m, 1H, CH of cyclohexyl), 3.03 (dd, J_1 = 11.4 Hz and J_2 = 4.0 Hz, 1H, 1H of CH_2O), 3.27 (dd, J_1 = 11.4 Hz and J_2 = 7.7 Hz, 1H, 1H of CH_2O), 3.58 and 3.80 (2d, J = 13.9 Hz, 2H, $PhCH_2N$), 3.92 (d, J = 8.1 Hz, 1H, H4), 4.12 (d, J = 2.2 Hz, 1H, H2), 4.14 (td, ABX system, 1H, H5), 7.09 (dd, J_1 = 6.6 Hz and J_2 = 2.2 Hz, 2H, 2 × CH of Ar), 7.22 (m, 5H, CH of Ar), 7.42 (d, J = 8.4 Hz, 2H, 2 × CH of Ar). ^{13}C NMR ($CDCl_3$): 25.5, 26.0, 26.7, 29.8, 30.3, 40.1, 54.7, 63.2, 67.7, 78.6, 99.0, 121.4, 127.2, 128.0 (2C), 129.2 (2C), 129.9 (2C), 131.3 (2C), 136.7 (2C). MS: Calcd for $C_{23}H_{29}BrNO_2$ $[M + H]^+$: 430.2. Found: 430.1. Purity LCMS: >98% (rt: 2.43 min).

5Cba: ^{1}H NMR ($CDCl_3$): 0.81 (t, J = 7.1 Hz, 3H, CH_3 of hexyl), 1.0−1.4 (m, 14H, CH_2 of hexyl and CH_3 of isopropyl), 1.92 (m, 1H, C*H*$(CH_3)_2$), 2.50 (m, 2H, CH_2N), 3.03 (dd, J_1 = 11.6 Hz and J_2 = 4.0 Hz, 1H, 1H of CH_2O), 3.20 (dd, J_1 = 11.6 Hz and J_2 = 7.9 Hz, 1H, 1H of CH_2O), 3.90 (d, J = 8.3 Hz, 1H, H4), 4.07 (d, J = 2.8 Hz, 1H, H2), 4.18 (td, J_1 = 8.1 Hz, J_2 = 7.9 Hz, J_3 = 4.0 Hz, 1H, H5), 7.26 (d, J = 8.4 Hz, 2H, 2 × CH of Ar), 7.42 (d, J = 8.4 Hz, 2H, 2 × CH of Ar). ^{13}C NMR ($CDCl_3$): 13.9, 15.0, 19.1, 22.5, 27.1, 28.0, 30.6, 31.5, 51.8, 63.3, 69.0, 79.0, 99.6, 121.2, 129.8 (2C), 131.2 (2C), 138.6. MS: Calcd for $C_{19}H_{31}BrNO_2$ $[M + H]^+$: 384.2. Found: 384.2. Purity LCMS: >98% (rt: 2.32 min).

5Cbb: ^{1}H NMR ($CDCl_3$): 0.80 (t, J = 7.0 Hz, 3H, CH_3 of hexyl), 0.91 (t, J = 7.2 Hz, 3H, CH_3 of hexyl), 1.0−1.9 (m, 18H, CH_2 of both hexyl groups), 2.51 (m, 2H, CH_2N), 3.09 (dd, J_1 = 11.6 Hz and J_2 = 4.0 Hz, 1H, 1H of CH_2O), 3.17 (dd, J_1 = 11.6 Hz and J_2 = 7.7 Hz, 1H, 1H of CH_2O), 3.87 (d, J = 7.9 Hz, 1H, H4), 4.17 (m, 2H, H5 and H2), 7.22 (d, J = 8.4 Hz, 2H, 2 × CH of Ar), 7.42 (d, J = 8.4 Hz, 2H, 2 × CH of Ar). ^{13}C NMR ($CDCl_3$): 14.0 (2C) 22.5 (2C), 24.6, 27.0, 28.3, 29.5, 31.5, 31.9, 34.7, 51.9, 63.2, 68.8, 79.6, 96.2, 121.2, 129.7 (2C), 131.2 (2C), 138.8. MS: Calcd for $C_{22}H_{37}BrNO_2$ $[M + H]^+$: 426.2. Found: 426.2. Purity LCMS: >95% (rt: 2.39 min).

5Cbc: ^{1}H NMR ($CDCl_3$): 0.81 (m, 5H, CH_3 of hexyl and 4-CH_2 of cyclohexyl), 1.0−1.9 (m, 16H, CH_2 of hexyl and CH_2 of cyclohexyl), 2.05 (m, 1H, CH of cyclohexyl), 2.50 (m, 2H, CH_2N), 3.03 (dd, J_1 = 11.7 Hz and J_2 = 4.0 Hz, 1H, 1H of CH_2O), 3.18 (dd, J_1 = 11.7 Hz and J_2 = 7.9 Hz, 1H, 1H of CH_2O), 3.87 (d, J = 8.1 Hz, 1H, H4), 4.03 (d, J = 2.6 Hz, 1H, H2), 4.15 (td, J_1 = 8.1 Hz, J_2 = 7.9 Hz, J_3 = 4.0 Hz, 1H, H5), 7.24 (d, J = 8.4 Hz, 2H, 2 × CH of Ar), 7.42 (d, J = 8.4 Hz, 2H, 2 × CH of Ar). ^{13}C NMR ($CDCl_3$): 14.0, 22.5, 25.8, 26.2, 26.7, 26.8, 27.1, 28.0, 29.8, 31.5, 40.9, 51.9, 63.2, 68.8, 79.2, 99.4, 121.2, 129.8 (2C), 131.2 (2C), 138.8. MS: Calcd for $C_{22}H_{35}BrNO_2$ $[M + H]^+$: 424.2. Found: 424.2. Purity LCMS: >98% (rt: 2.54 min).

5Cca: ^{1}H NMR ($CDCl_3$): 0.70 and 0.76 (2d, J = 6.6 Hz, 6H, 2 × CH_3 of isobutyl), 1.07 and 1.09 (2d, J = 6.6 and 7.0 Hz, 6H, 2 × CH_3 of isopropyl), 1.43 (m, 1H, C*H*$(CH_3)_2$), 1.94 (m, 1H, C*H*$(CH_3)_2$), 2.23 (dd, J_1 = 12.5 Hz and J_2 = 9.1 Hz, 1H, 1H of CH_2N), 2.35 (dd, J_1 = 12.5 Hz and J_2 = 5.9 Hz, 1H, 1H of CH_2N), 3.06 (dd, J_1 = 11.7 Hz and J_2 = 4.0 Hz, 1H, 1H of CH_2O), 3.21 (dd, J_1 = 11.7 Hz and J_2 = 7.9 Hz, 1H, 1H of CH_2O), 3.77 (d, J = 8.1 Hz, 1H, H4), 3.99 (d, J = 2.9 Hz, 1H, H2), 4.18 (ABX system, 1H, H5), 7.25 (d, J = 8.4 Hz, 2H, 2 × CH of Ar), 7.41 (d, J = 8.4 Hz, 2H, 2 × CH of Ar);^{13}C NMR ($CDCl_3$): 15.3, 19.3, 20.7, 21.2, 27.6, 30.9, 62.5, 63.1, 70.5, 79.4, 100.6, 121.2, 129.8 (2C), 131.1 (2C), 139.4. MS: Calcd for $C_{17}H_{27}BrNO_2$ $[M + H]^+$: 356.1. Found: 356.2. Purity LCMS: >98% (rt: 2.27 min).

5Ccb: ^{1}H NMR ($CDCl_3$): 0.69 and 0.77 (2d, J = 6.6 and 7.0 Hz, 6H, 2 × CH_3 of isobutyl), 0.90 (t, J = 7.0 Hz, 3H, CH_3 of hexyl), 1.1−1.8 (m, 11H, CH_2 of hexyl and C*H*$(CH_3)_2$), 2.22 (dd, J_1 = 12.5 Hz and J_2 = 9.9 Hz, 1H, 1H of CH_2N), 2.37 (dd, J_1 = 12.5 Hz and J_2 = 5.5 Hz, 1H, 1H of CH_2N), 3.10 (dd, J_1 = 11.7 Hz and J_2 = 4.0 Hz, 1H, 1H of CH_2O), 3.16 (dd, J_1 = 11.7 Hz and J_2 = 7.7 Hz, 1H, 1H of CH_2O), 3.77 (d, J = 7.7 Hz, 1H, H4), 4.13 (dd, J_1 = 7.3 Hz and J_2 = 2.2 Hz, 1H, H2), 4.17 (td, J_1 = 7.7 Hz, J_2 = 7.7 Hz, J_3 = 4.0 Hz, 1H, H5), 7.22 (d, J = 8.4 Hz, 2H, 2 × CH of Ar), 7.41 (d, J = 8.4 Hz, 2H, 2 × CH of Ar). ^{13}C NMR ($CDCl_3$): 14.1, 20.6, 20.9, 22.6, 24.8, 27.6, 29.5, 31.9, 34.9, 62.0, 63.0, 70.1, 79.9, 97.1, 121.1, 129.8 (2C), 131.1 (2C), 139.4. MS: Calcd for $C_{20}H_{33}BrNO_2$ $[M + H]^+$: 398.2. Found: 398.2. Purity LCMS: >98% (rt: 2.53 min).

5Ccc: ^{1}H NMR ($CDCl_3$): 0.69 and 0.75 (2d, J = 6.5 and 6.8 Hz, 6H, 2 × CH_3 of isobutyl), 1.0−1.9 (m, 11H, CH_2 of cyclohexyl and C*H*$(CH_3)_2$), 2.13 (m, 1H, CH of cyclohexyl), 2.24 (dd, J_1 = 12.3 Hz and J_2 = 9.1 Hz, 1H, 1H of CH_2N), 2.33 (dd, J_1 = 12.3 Hz and J_2 = 5.1 Hz, 1H, 1H of CH_2N), 3.06 (dd, J_1 = 11.7 Hz and J_2 = 4.1 Hz, 1H, 1H of CH_2O), 3.22 (m, 1H, 1H of CH_2O), 3.75 (d, J = 7.9 Hz, 1H, H4), 3.95 (d, J = 2.6 Hz, 1H, H2), 4.16 (td, J_1 = 8.0 Hz, J_2 = 7.7 Hz, J_3 = 4.0 Hz, 1H, H5), 7.23 (d, J = 8.4 Hz, 2H, 2 × CH of Ar), 7.40 (d, J = 8.4 Hz, 2H, 2 × CH of Ar). ^{13}C NMR ($CDCl_3$): 20.6, 21.1, 26.0, 26.2, 26.8, 27.6, 29.9, 30.2, 41.1, 62.5, 63.0, 70.2, 79.5, 100.3, 121.0, 129.8 (2C), 131.0 (2C), 139.5. MS: Calcd for $C_{20}H_{31}BrNO_2$ $[M + H]^+$: 396.2. Found: 396.2. Purity LCMS: 87% (rt: 2.48 min).

5Cda: ^{1}H NMR ($CDCl_3$): 0.97 and 1.02 (2d, J = 6.6 and 7.3 Hz, 6H, 2 × CH_3 of isopropyl), 1.75 (m, 1H, C*H*$(CH_3)_2$),

3.02 (dd, $J_1 = 11.5$ Hz and $J_2 = 4.0$ Hz, 1H, 1H of CH_2O), 3.28 (dd, $J_1 = 11.5$ Hz and $J_2 = 7.9$ Hz, 1H, 1H of CH_2O), 3.55 and 3.72 (2d, $J = 13.9$ Hz, 2H, $ArCH_2N$), 3.77 (s, 3H, CH_3O), 3.94 (d, $J = 8.1$ Hz, 1H, H4), 4.14 (m, 2H, H5 and H2), 6.74 (d, $J = 8.8$ Hz, 2H, 2 × CH of Ar), 6.97 (d, $J = 8.8$ Hz, 2H, 2 × CH of Ar), 7.22 (d, $J = 8.4$ Hz, 2H, 2 × CH of Ar), 7.41 (d, $J = 8.4$ Hz, 2H, 2 × CH of Ar). ^{13}C NMR ($CDCl_3$): 14.6, 19.1, 29.6, 53.4, 55.2, 63.3, 67.4, 78.3, 98.6, 113.4 (2C), 121.3, 128.4, 129.8 (2C), 129.9 (2C), 131.3 (2C), 136.6, 158.8. MS: Calcd for $C_{21}H_{27}BrNO_3$ $[M + H]^+$: 420.1. Found: 420.2. Purity LCMS: >98% (rt: 2.17 min).

5Cdb: ^1H NMR ($CDCl_3$): 0.89 (t, $J = 7.1$ Hz, 3H, CH_3 of hexyl), 1.2−1.7 (m, 10H, CH_2 of hexyl), 3.08 (dd, $J_1 = 11.6$ Hz and $J_2 = 4.0$ Hz, 1H, 1H of CH_2O), 3.25 (dd, $J_1 = 11.6$ Hz and $J_2 = 7.3$ Hz, 1H, 1H of CH_2O), 3.54 and 3.75 (2d, $J = 14$ Hz, 2H, $ArCH_2N$), 3.77 (s, 3H, CH_3O), 3.93 (d, $J = 8.1$ Hz, 1H, H4), 4.14 (ABX system, 1H, H5), 4.26 (dd, $J_1 = 6.3$ Hz and $J_2 = 2.1$ Hz, 1H, H2), 6.75 (d, $J = 8.6$ Hz, 2H, 2 × CH of Ar), 7.00 (d, $J = 8.6$ Hz, 2H, 2 × CH of Ar), 7.23 (d, $J = 8.4$ Hz, 2H, 2 × CH of Ar), 7.43 (d, $J = 8.4$ Hz, 2H, 2 × CH of Ar). ^{13}C NMR ($CDCl_3$): 14.1, 22.6, 24.1, 29.3, 31.8, 34.0, 53.5, 55.2, 63.3, 67.6, 78.9, 95.4, 113.5 (2C), 121.4, 128.7, 129.9 (2C), 130.3 (2C), 131.4 (2C), 136.6, 158.8. MS: Calcd for $C_{24}H_{33}BrNO_3$ $[M + H]^+$: 462.2. Found: 462.2. Purity LCMS: >98% (rt: 2.35 min).

5Cdc: ^1H NMR ($CDCl_3$): 0.93 (t_{app}, $J = 7.3$ Hz, 2H, 4-CH_2 of cyclohexyl), 1.0−1.9 (m, 8H, CH_2 of cyclohexyl), 1.96 (m, 1H, CH of cyclohexyl), 3.02 (dd, $J_1 = 11.4$ Hz and $J_2 = 4.0$ Hz, 1H, 1H of CH_2O), 3.26 (dd, $J_1 = 11.7$ Hz and $J_2 = 7.7$ Hz, 1H, 1H of CH_2O), 3.55 and 3.72 (2d, $J = 13.9$ Hz, 2H, $ArCH_2N$), 3.76 (s, 3H, CH_3O), 3.90 (d, $J = 8.1$ Hz, 1H, H4), 4.11 (d, $J = 2.2$ Hz, 1H, H2), 4.12 (ABX system, 1H, H5), 6.74 (d, $J = 8.6$ Hz, 2H, 2 × CH of Ar), 6.98 (d, $J = 8.6$ Hz, 2H, 2 × CH of Ar), 7.21 (d, $J = 8.4$ Hz, 2H, 2 × CH of Ar), 7.41 (d, $J = 8.4$ Hz, 2H, 2 × CH of Ar). ^{13}C NMR ($CDCl_3$): 25.4, 26.1, 26.7, 26.8, 29.8, 40.0, 53.6, 55.3, 63.2, 67.3, 78.5, 98.5, 113.3 (2C), 121.3, 128.5, 130.0 (2C), 130.4 (2C), 131.3 (2C), 136.7, 158.8. MS: Calcd for $C_{24}H_{31}BrNO_3$ $[M + H]^+$: 460.2. Found: 460.2. Purity LCMS: >98% (rt: 2.35 min).

Acknowledgment. This work was supported by the NIH (GM56154, K.D.J.), The Skaggs Institute for Chemical Biology (K.D.J.), Aventis Pharmaceutical Company (K.D.J. and P.W.), and NSERC (Natural Sciences and Engineering Research Council of Canada, for a fellowship to M.R.T). The authors also thank Dr. William A. Metz of Aventis Research Center for coordinating the Aventis−Scripps collaboration.

Supporting Information Available. Spectra of products. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) Houghten, R. A.; Pinilla, C.; Blondelle, S. E.; Appel, J. R.; Dooley, C. T.; Cuervo, J. H. *Nature* **1991**, *354*, 84−86.
(2) Jung, G.; Beck-Sickinger, A. G. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 367−383.
(3) Han, H.; Wolfe, M. M.; Brenner, S.; Janda, K. D. *Proc. Natl. Acad. Sci. U.S.A.* **1995**, *92*, 6419−6423.
(4) Ecker, D. J.; Vickers, T. A.; Hanecak, R.; Driver, V.; Anderson, K. *Nucleic Acids Res.* **1993**, *21*, 1853−1856.
(5) Zheng, C.; Seeberger, P. H.; Danishefsky, S. J. *J. Org. Chem.* **1998**, *63*, 1126−1130.
(6) Wentworth, P., Jr.; Janda, K. D. *Curr. Opin. Biotech.* **1998**, *9*, 109−115.
(7) Thompson, L. A.; Ellman, J. A. *Chem. Rev.* **1996**, *96*, 555−600.
(8) Norman, T. C.; Gray, N. S.; Koh, J. T.; Schultz, P. G. *J. Am. Chem. Soc.* **1996**, *118*, 7430−7431.
(9) Stankova, M.; Lebl, M. *Mol. Diversity* **1996**, *2*, 75−80.
(10) Nugiel, D. A.; Cornelius, L. A. M.; Corbett, J. W. *J. Org. Chem.* **1997**, *62*, 201−203.
(11) Wong, C.-H.; Ye, X.-S.; Zhang, Z. *J. Am. Chem. Soc.* **1998**, *120*, 7137−7138.
(12) Hirschmann, R.; Nicolaou, K. C.; Pietranico, S.; Salvino, J.; Leahy, E. M.; Sprengeler, P. A.; Furst, G.; Smith, A. B., III. *J. Am. Chem. Soc.* **1992**, *114*, 9217−9218.
(13) Hirschmann, R.; Sprengeler, R. A.; Kawasaki, T.; Leahy, J. W.; Shakespeare, W. C.; Smith, A. B., III. *J. Am. Chem. Soc.* **1992**, *114*, 9699−9701.
(14) Kocis, P.; Issakova, O.; Sepetove, N.; Lebl, M. *Tetrahedron Lett.* **1995**, *36*, 6623−6626.
(15) Carell, T.; Wintner, E. A.; Bahir-Hashemi, A.; Rebek, J., Jr. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2059−2061.
(16) Scolastico, C. *Pure Appl. Chem.* **1988**, *60*, 1689−1698.
(17) Hoppe, I.; Hoffmann, H.; Gärtner, I.; Krettek, T.; Hoppe, D. *Synthesis* **1991**, 1157−1162.
(18) Agami, C.; Couty, F.; Lam, H.; Mathieu, H. *Tetrahedron* **1998**, *54*, 8783−8786.
(19) Agami, C.; Couty, F.; Venier, O. *Synlett* **1995**, 1027−1028.
(20) Agami, C.; Comesse, S.; Kadouri-Puchot, C.; Lusinchi, M. *Synlett* **1999**, 1094−1096.
(21) Agami, C.; Couty, F.; Evano, G.; Mathieu, H. *Tetrahedron* **2000**, *56*, 367−376.
(22) Agami, C.; Dechoux, L.; Melaimi, M. *Org. Lett.* **2000**, *2*, 633−634.
(23) Moloney, G. P.; Craik, D. J.; Iskander, M. N.; Nero, T. L. *J. Chem. Soc., Perkin Trans. 2* **1998**, 199−206.
(24) Hoppe, I.; Hoppe, D.; Wolff, C.; Egert, E.; Herbst, R. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 67−69.
(25) Neelakantan, L. *J. Org. Chem.* **1971**, *36*, 2256−2260.
(26) Arséniyadis, S.; Huang, P. Q.; Morellet, N.; Beloeil, J.-C.; Husson, H.-P. *Heterocycles* **1990**, *31*, 1789−1799.
(27) Takahashi, H.; Hsieh, B. C.; Higashiyama, K. *Chem. Pharm. Bull.* **1990**, *38*, 2429−2434.
(28) Beckett, A. H.; Jones, G. R. *Tetrahedron* **1977**, *33*, 3313−3316.
(29) Just, G.; Potvin, P.; Uggowitzer, P.; Bird, P. *J. Org. Chem.* **1983**, *48*, 2923−2924.
(30) Agami, C.; Rizk, T. *Tetrahedron* **1985**, *41*, 537−540.
(31) Hanson, R. M. *Chem. Rev.* **1991**, *91*, 437−474.
(32) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974−5976.
(33) Cernerud, M.; Reina, J. A.; Tegenfeld, J.; Moberg, C. *Tetrahedron: Asymmetry* **1996**, *7*, 2863−2870.
(34) Chini, M.; Crotti, P.; Macchia, F. *J. Org. Chem.* **1991**, *56*, 5939−5942.
(35) Vidal-Ferran, A.; Bampos, N.; Moyano, A.; Pericas, M. A.; Riera, A.; Sanders, J. K. M. *J. Org. Chem.* **1998**, *63*, 6309−6318.
(36) Payne, G. B. *J. Org. Chem.* **1962**, *27*, 3819−3822.
(37) Barlos, K.; Gatos, D.; Kallitsis, J.; Papaphotiu, G.; Sotiriu, P.; Wenging, Y.; Shäfer, W. *Tetrahedron Lett.* **1989**, *30*, 3943−3946.
(38) Thompson, L. A.; Ellman, J. A. *Tetrahedron Lett.* **1994**, *35*, 9333−93336.
(39) Hu, Y.; Porco, J. A., Jr.; Labadie, J. W.; Gooding, O. W.; Trost, B. M. *J. Org. Chem.* **1998**, *63*, 4518−4521.
(40) Hu, Y.; Porco, J. A., Jr. *Tetrahedron Lett.* **1998**, *39*, 2711−2714.

(41) Lorgé, F.; Wagner, A.; Mioskowski, C. *J. Comb. Chem.* **1999**, *1*, 25−27.
(42) Merino, P.; Castillo, E.; Merchan, F. L.; Tejero, T. *Tetrahedron: Asymmetry* **1997**, *8*, 1725−1729.
(43) Andrés, J. M.; Barrio, R.; Martinez, M. A.; Pedrosa, R.; Pérez-Encabo, A. *J. Org. Chem.* **1996**, *61*, 4210−4213.
(44) Just, G.; Luthe, C.; Potvin, P. *Tetrahedron Lett.* **1982**, *23*, 2285−2290.
(45) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765−5780.
(46) Vidal-Ferran, A.; Moyano, A.; Pericas, M. A.; Riera, A. *J. Org. Chem.* **1997**, *62*, 4970−4982.
(47) Laïb, T.; Chastanet, J.; Zhu, J. *J. Org. Chem.* **1998**, *63*, 1709−1713.

CC0000500