ORGANIC LETTERS

1999
Vol. 1, No. 5
807−810

A Facile Method for the Solution and Solid-Phase Synthesis of Substituted [3.3.1] Bicycles

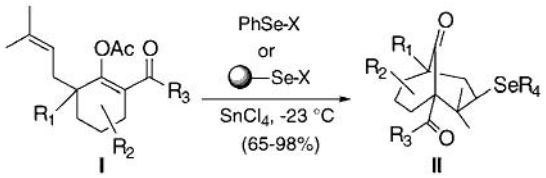
K. C. Nicolaou,* Jeffrey A. Pfefferkorn, Guo-Qiang Cao, Sanghee Kim, and Jilali Kessabi

Department of Chemistry and The Skaggs Institute for Chemical Biology, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, California 92037, and Department of Chemistry and Biochemistry, University of California, San Diego, 9500 Gilman Drive, La Jolla, California 92093

kcn@scripps.edu

Received July 7, 1999

ABSTRACT



Interest in bicyclic natural products from the Guttiferae classification has led to the development of an improved method for the selenium-mediated cyclization of alkenyl-substituted β-dicarbonyls (I) to form a variety of bicyclo[3.3.1]nonan-9-ones (II) both in solution and on solid support.

Garsubellin A (**1**, Figure 1) is a polyisoprenylated phloroglucinol derivative from *Garcinia subelliptica* found on the Okinawa Islands of Japan.[1] It is characterized by a highly oxygenated and densely substituted bicyclo[3.3.1]nonane-1,3,5-trione core fused to a tetrahydrofuran ring and appended with lipophilic side chains. Interest in garsubellin A (**1**) stems from its in vitro neurotrophic properties making it a potential candidate for the treatment of neurodegenerative diseases.[2] The potential importance of garsubellin A (**1**) to biology and medicine prompted us to pursue a total synthesis,[3] the success of which was contingent upon developing a reliable methodology for constructing its unusual bicyclic skeleton. Moreover, since the core of garsubellin A (**1**) is conserved among a number of other natural products of the Guttiferae classification,[4] including nemorosone II[5] (**2**), a versatile construction of this framework might find application in future synthetic investigations of this biologically diverse

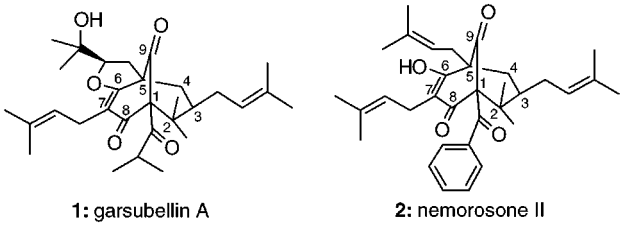


Figure 1. Structure of garsubellin A (**1**) and nemorosone II (**2**).

family of compounds. Herein we describe an improved method for the construction of the 2,2-dimethylbicyclo[3.3.1]-nonan-9-one carbon framework of these molecules.

From a synthetic vantage point, one of the challenging features of this skeleton is the highly congested C-1 through C-3 region (Figure 1) with a quaternary *gem*-dimethyl group at C-2 flanked by a quaternary bridgehead carbon (C-1) and a tertiary prenylated carbon (C-3). This congestion, compounded by the fact that the remaining bridgehead position (C-5) is also quaternary, essentially precludes construction

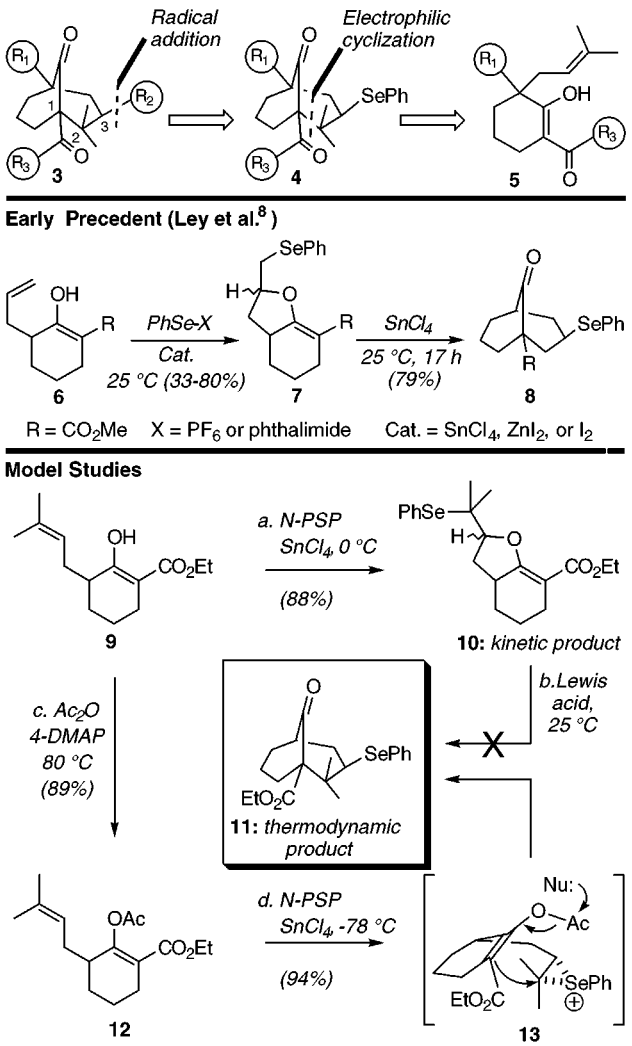
(1) Fukuyama, Y.; Kuwayama, A.; Minami, H. *Chem. Pharm. Bull.* **1997**, *45*, 947−949.
(2) Hefti, F. J. *Annu. Rev. Pharmcol. Toxicol.* **1997**, *37*, 239−267. Hefti, F. J. *Neurobiol.* **1994**, 1418−1435.
(3) Nicolaou, K. C.; Pfefferkorn, J. A.; Kim, S.; Wei, H. *J. Am. Chem. Soc.* **1999**, *121*, 4724−4725.

10.1021/ol990791d CCC: $18.00
Published on Web 08/06/1999

of this framework via the α,α′-annulation strategies traditionally employed in the construction of bicyclo[3.3.1]nonan-9-ones.[6] In fact, there has been very little work reported on the synthesis of 2,2-dimethylbicyclo[3.3.1]nonan-9-ones with both bridgehead positions substituted as required for construction of the garsubellin A (**1**) skeleton.[7] In light of this, we considered a strategy as outlined in the simplified retrosynthetic analysis of Scheme 1. Examination of the general skeleton **3** led to the realization that the C-3 substituent might be disconnected via a radical addition transform leading to intermediate **4** which revealed the retron for a powerfully simplifying selenium-induced endocyclization of a pendent olefin onto a suitably positioned β-dicarbonyl moiety. Such a cyclization would establish, in one step, the bicycle through construction of the sterically demanding C-1−C-2 bond with concomitant installation of a radical precursor at C-3. Encouragingly, as shown in Scheme 1, Ley et al. had previously accomplished the construction of bicycle **8** by treatment of an allyl-substituted β-keto ester **6** with a variety of selenium donors and catalysts to initially afford the kinetically favored *O*-cyclized furan **7**, which was subsequently equilibrated to the thermodynamically favored carbocycle **8**.[8] Thus, we constructed the corresponding prenylated β-keto ester model system **9** (Scheme 1) and using similar conditions, obtained the *O*-cyclized furan **10** in 88% yield. Unfortunately, furan **10** proved resistant toward equilibration to the desired 2,2-dimethylbicyclo[3.3.1]nonan-9-one **11** even upon prolonged exposure (24 h) to a variety of Lewis acids (see Scheme 1) resulting only in decomposition. This failure forced us to consider a strategy for masking the nucleophilicity of the enolic oxygen, thereby providing direct access to the desired carbocyclic product. We postulated that acetylation of the enolic oxygen would inhibit *O*-cyclization[9] and, as proposed in intermediate **13**, might lead to the desired *C*-cyclization through *in situ*, nucleophilically assisted cleavage of the acetate during carbon-centered attack on a pendent *epi*-selenium complex. To test this hypothesis, we prepared enol acetate **12**, and gratifyingly, upon treatment with *N*-(phenylseleno)phthalimide (*N*-PSP)[10] and $SnCl_4$ at −78 °C for 5 min, it underwent exclusive conversion to the desired carbocycle **11**, in 94% yield.

Encouraged by the facility and selectivity of this cyclization at low temperature, we sought to determine its synthetic utility focusing on three criteria: (a) tolerance toward increasing substitution on the cyclohexane framework as required for the construction of various natural and designed products; (b) effect of olefin substitution on the regioselec-

Scheme 1. General Retrosynthetic Analysis and Model Studies of Selenium-Mediated Cyclizations[a]



[a] Conditions: (a) 1.1 equiv of *N*-PSP, 1.0 equiv of $SnCl_4$, CH_2Cl_2, 0 °C 10 min; (b) 1.1 equiv of ($SnCl_4$, $TiCl_4$, $ZnCl_2$, $AlCl_3$, or BF_3OEt_2), CH_2Cl_2, 0 to 25 °C, 24 h; (c) Ac_2O, 4-DMAP, 80 °C, 30 min; (d) 1.1 equiv of *N*-PSP, 1.0 equiv of $SnCl_4$, CH_2Cl_2, −78 °C, 5 min. Abbreviations: 4-DMAP = 4-(dimethylamino)pyridine. *N*-PSP = *N*-(phenylseleno)phthalimide.

(4) For examples, see: Gustafson, K. R.; Blunt, J. W.; Munro, M. H. G.; Fuller, R. W.; McKee, T. C.; Cardelina, J. H.; McMahon, J.; Gragg, G. M.; Boyd, M. R. *Tetrahedron* **1992**, *48*, 10093−10102. Iinuma, M.; Tosa, H.; Tanaka, T.; Kanamaru, S.; Asai, F.; Kobayashi, Y.; Miyauchi, K.; Shimano, R. *Biol. Pharm. Bull.* **1996**, *18*, 311−314. Alves, T. M .A.; Alves, R. O.; Romanha, A. J.; Santos, M. H.; Nagem, T. J.; Zani, C. L. *J. Nat. Prod.* **1999**, *62*, 369−371. Oliveira, C. M. A.; Porto, A. M.; Bittrich, V.; Vencato, I.; Marsaioli, A. J. *Tetrahedron Lett.* **1996**, *37*, 6427−6430.

(5) Oliveira, C. M. A.; Porto, A. L. M.; Bittrich, V.; Marsaioli, A. J. *Phytochemistry* **1999**, *50*, 1073−1079.

(6) For examples, see: Taeschler, C.; Sorenson, T. S. *J. Org. Chem.* **1998**, *63*, 5704−5705. Harding, K. E.; Clement, B. A.; Moreno, L.; Katalinic, J. P. *J. Org. Chem.* **1981**, *46*, 940−948. Padwa, A.; Kline, D. N.; Murphree, S. S.; Yeske, P. E. *J. Org. Chem.* **1992**, *57*, 298−306. Peters, J. A. *Synthesis* **1979**, 321−336. Lu, X.; Huang, Y. *Tetrahedron Lett.* **1986**, *27*, 1615−1616.

(7) To the best of our knowledge, no substituted 2,2-dimethylbicyclo-[3.3.1]nonan-9-one wherein both bridgehead positions are quaternary has been reported. For examples of the construction of substituted 2,2-dimethylbicyclo[3.3.1]nonan-9-one with at least one quaternary bridgehead position, see: Firrel, N. F.; Hickmott, P. W.; Hopkins, B. J. *J. Chem Soc. C* **1970**, 1477−1480. Dauben, W. G.; Bunce, R. A. *J. Org. Chem.* **1983**, *48*, 4642−4648. Gambacorta, A.; Fabrizi, G.; Bovicelli, P. *Tetrahedron* **1992**, *48*, 4459−4464. Evans, E. H.; Hewson, A. T.; March, L. A.; Nowell, I. W.; Wadsworth, A. H. *J. Chem. Soc., Perkin Trans. 1* **1987**, 137−149.

(8) Jackson, W. P.; Ley, S. V.; Morton, J. A. *J. Chem. Soc., Chem. Commun.* **1980**, 1028−1029. Jackson, W. P.; Ley, S. V.; Whittle, A. J. *J. Chem. Soc., Chem. Commun.* **1980**, 1173−1174. Jackson, W. P.; Ley, S. V.; Morton, J. A. *Tetrahedron Lett.* **1981**, *22*, 2601−2604.

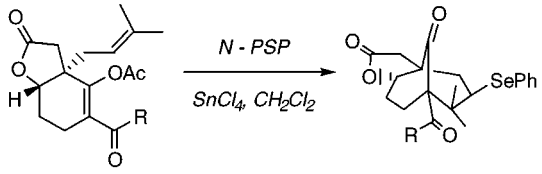
(9) For precedent, see: Edstrom, E. D.; Livinghouse, T. *J. Org. Chem.* **1987**, *52*, 951−953. Tamelen, E. E; Hwu, J. R.; Leiden, T. M. *J. Chem. Soc., Chem. Commun.* **1983**, 62−63. Evans, E. H.; Hewson, A. T.; Wadsworth, A. H. *Synth. Comm.* **1985**, *15*, 243−247.

(10) Nicolaou, K. C.; Claremon, D. A.; Barnette, W. E.; Seitz, S. P. *J. Am. Chem. Soc.* **1979**, *101*, 3704−3706. Nicolaou, K. C.; Petasis, N. A.; Claremon, D. A. *Tetrahedron* **1985**, *41*, 4835−4841.

tivity of the cyclization; and (c) applicability of solid-phase selenium reagents,[11] thereby allowing for construction of resin-bound bicycles applicable to solid-phase natural product and combinatorial synthesis.

We began by exploring the effects of increased substrate functionalization with an emphasis on constructing suitable frameworks for the total synthesis of garsubellin A (**1**), nemorosone II (**2**), and related natural products. Of primary interest were the lactone-functionalized systems of Table 1

Table 1. Construction of Frameworks for Bicyclic Natural Products from the Guttiferae Classification



substrate	R	temp(°C)	time(min)	yield(%) [a]
14	OMe	-23	5	95
15	Me	-23	5	93
16	*i*-Pr	-10	15	80[b]
17	Ph	-23	10	85
18	$CH{=}CMe_2$	-23	15	62

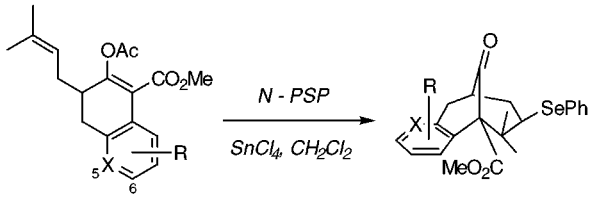
[a] Isolated yield after purification unless otherwise noted. [b] Yield at 40% conversion by ^{1}H NMR of crude reaction mixture.

since the bicyclic products resulting from such substrates possessed the minimum functionality required for elaboration to these compounds (**1** and **2**), as we recently demonstrated by converting the product of substrate **14** to the fully substituted and oxygenated core of garsubellin A (**1**).[3] As illustrated in Table 1, the cyclization was not hampered by the increased strain introduced by the fused lactone, and it nicely accommodated a variety of substituents including methoxy, methyl, isopropyl, phenyl, and even a conjugated olefin. Unlike the previous model systems, these more functionalized substrates required slightly higher temperatures (−23 °C) for optimal conversion. The only limitation noted was with substrate **16** as the increased steric demand of the isopropyl substituent caused the reaction to proceed sluggishly and never past 40% conversion. Attempts to increase conversion using higher reaction temperatures or longer reaction times resulted only in decomposition.

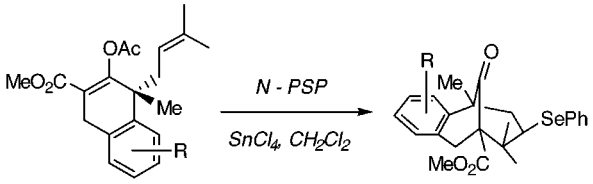
Cognizant of the presence of [3.3.1] bicycles in a host of other bioactive natural and designed structures, we sought to extend our studies. As an example we considered construction of a variety of fused aromatic bicycles such as those shown in Table 2. Since several natural products (e.g., selagine[12] and huperzine[13]) as well as several designed small molecule analgesics[14] and anticonvulsants[15] possess related skeletons, application of the current methodology would allow for the construction of conformationally constrained analogues.[16] As shown in Table 2, the cyclization reaction

(11) Nicolaou, K. C.; Pastor, J.; Barluenga, S.; Winssinger, N. *Chem. Commun.* **1998**, 1947−1948. We thank N. Winssinger for the generous preparation of a sample of these resins.

Table 2. Construction of Aryl-Fused Bicyclo[3.3.1]nonan-9-ones via Selenium-Mediated Cyclizations



substrate	R	X	temp(°C)	time(min)	yield(%) [a]
19	H	C	-23	15	90
20	5-OMe	C	-23	10	78
21	6-OMe	C	-23	5	89
22	6-OMe	N	-23	15	21 [b]



substrate	R	temp(°C)	time(min)	yield(%) [a]
23	H	-23	5	98
24	6-OMe	-23	10	95

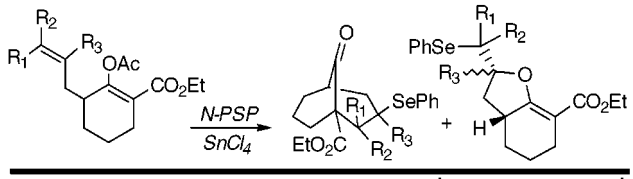
[a] Isolated yield after purification unless otherwise noted. [b] Yield determined ^{1}H NMR of crude reaction mixture.

is generally tolerant of even electron-rich aromatics, although the product of substrate **22** was obtained only in low yield.

Notwithstanding the utility of these substituted 2,2-dimethylbicyclo[3.3.1]nonan-9-ones, we hoped to expand the usefulness of this cyclization by varying the substitution of the olefin, thereby accommodating the construction of differentially substituted bicycles. Preliminarily, we sought to determine the effect (if any) that olefin substitution had on the regioselectivity of the cyclization. As illustrated in Table 3, we returned to the original model system, varying the alkenyl substituents.

Quite unexpectedly, these substituent changes caused a dramatic perturbation in cyclization selectivity. In fact, in

Table 3. Effects of Olefin Substitution on Cyclization Regioselectivity[a]



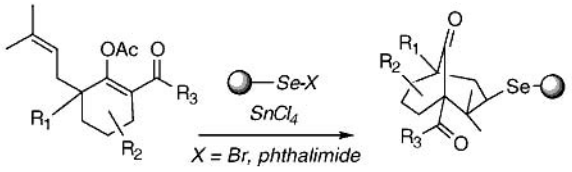
substrate	R_1	R_2	R_3	*C*-Cyclized (%) [b]	*O*-Cyclized (%) [b]
25	H	H	H	0	91 [c]
26	H	Me	H	45	41 [c]
12	Me	Me	H	94	0
27	H	H	Me	0	64 [c]
28	H	Me	Me	0	89
29	Me	Me	Me	0	86

[a] Reaction conditions: 1.1 equiv of *N*-PSP, 1.0 equiv of $SnCl_4$, CH_2Cl_2, −23 °C, 15 min. [b] Isolated yield after purification unless otherwise noted. [c] Yield as a mixture of stereoisomers.

all cases, except for the original model **12** and the crotyl substituted system **26**, the valuable preference for carbon-centered cyclization was lost. Although a complete explanation of these results remains elusive, we have excluded the possibility that the substrates may be suffering cleavage of the enol acetate functionality prior to cyclization, as substrates treated with $SnCl_4$ under the same conditions but in the absence of *N*-PSP were recovered in greater than 90% yield in all cases. Hence, the results may be attributed to the sterics governing approach of the *epi*-selenium complex to the nucleophilic center.[17]

Last, with an improved understanding of the potential and limits of this cyclization in hand, we turned our attention toward solid-phase applications of the method. We previously reported the construction of polystyrene-based selenium bromide and selenium phthalimide resins;[11] consequently, we sought to determine whether such cyclization reactions might be amenable to the construction of resin-bound bicycles. Initially, we considered the simplified enol acetate **12** (see structure in Scheme 1) as a substrate for both resins. By using slightly longer reaction times (Table 4) and a 3-fold excess of substrate and $SnCl_4$, **12** was independently reacted with each resin in CH_2Cl_2. Subsequently, the resins were treated with *n*-Bu_3SnH and AIBN at 80 °C to affect cleavage of any reaction products. Gratifyingly, the reaction with the selenium bromide resin cleanly yielded the desired bicycle in 89% yield on the basis of theoretical resin loading. In contrast, the reaction with the selenium phthalimide resin produced no detectable bicyclic products. With the success of the former reagent, we attempted the cyclization of several representative substrates as illustrated in Table 4. Solution and solid-phase behavior were closely correlated in all cases. Besides acting as a robust tether, the selenium linker can undergo traceless or functionalizing cleavage as shown in Scheme 2. The versatility of these cleavage options coupled with the economy of a single step loading/cyclization to produce resin-bound polyfunctionalized bicycles opens the possibility for the solid-phase synthesis of **1** and **2**, and more importantly, provides access to a novel class of rigid, carbocyclic scaffolds amenable to further combinatorial derivatization for the development of small molecule libraries.[18]

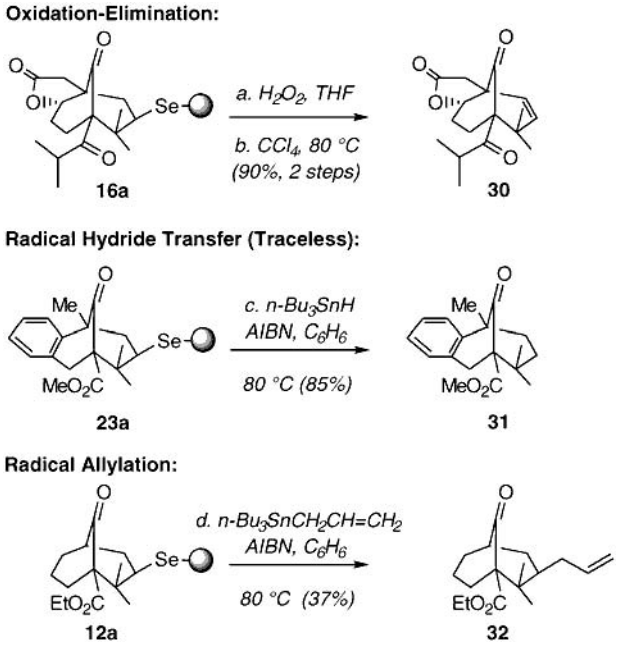
Table 4. Solid-Phase Cyclization Reactions[a]



substrate [b]	X	time(min)	loading(%) [c]	purity(%) [d]
12	Phthalimide	20	0	na
12	Phthalimide	40	0	na
12	Br	20	83	98
14	Br	20	91	98
16	Br	20	81	85
19	Br	20	85	98
21	Br	20	55	80
23	Br	20	87	98
24	Br	20	90	98

[a] Reaction conditions: 1.0 equiv of resin, 3.0 equiv of substrate, 3.0 equiv of $SnCl_4$, CH_2Cl_2, −23 °C. [b] See Scheme 1, Table 1, and Table 2 for structure of substrates. [c] Loading is approximated by mass gain of resin assuming a functionalization of 1.76 mmol/g. [d] Purity determined by ^1H NMR of crude cleavage product [via oxidation−elimination protocol (Scheme 2)].

Scheme 2. Cleavage Protocols of Selenium Linker[a]



[a] Conditions: (a) 10.0 equiv of 30% H_2O_2, THF, 0 °C, 2 h; (b) CCl_4, 80 °C, 10 min; (c) 5.0 equiv of *n*-Bu_3SnH, 0.1 equiv of AIBN, C_6H_6, 80 °C, 2 h; (d) 5.0 equiv of *n*-$Bu_3SnCH_2CH{=}CH_2$, 0.1 equiv of AIBN, C_6H_6, 80 °C, 2 h.

Acknowledgment. This work was supported by the National Institutes of Health, Bethesda, MD, The Skaggs Institute for Chemical Biology, and the Department of Defense (fellowship to J.P.).

Supporting Information Available: Representative procedures and spectral data for the preparation and cyclization of substrates **12**, **14** (solid phase), **15**, and **21**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL990791D

(12) Shamma, M.; Jones, C. D.; Weiss, J. A. *Tetrahedron* **1969**, *25*, 4743.
(13) Review: Kozikowski, A. P.; Tuckmantel, W. *Acc. Chem. Res.* **1999**, *32*, to appear in the August issue on p 641 and available via ACS Articles ASAP until print publication.
(14) Freed, M. E.; Potoski, J. R.; Freed, E. H.; Conklin, G. L. *J. Med. Chem.* **1973**, *16*, 595−599.
(15) Gilbert, I. M.; Hewett, C. L.; Ree, D. R.; Redpath, J.; Savage, D. S.; Sleigh, T. *J. Chem. Soc., Perkin Trans. 1* **1995**, 133−139.
(16) For an example of the utility of the *gem*-dimethyl group in huperzine analogs, see: Kozikowski, A. P.; Ding, Q.; Saxena, A.; Doctor, B. P. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 259−262.
(17) Molecular modeling studies are in progress.
(18) Gordon, E. M.; Barrett, R. W.; Dower, W. J.; Fodor, S. P. A.; Gallop, M. A. *J. Med. Chem.* **1994**, *37*, 1385−1401. For a similar example, see: Ley, S. V.; Mynett, D. M.; Koot, W. J. *Synlett* **1995**, 1017−1020.