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ω-Alkoxy analogues of SAHA (vorinostat) as inhibitors of HDAC: A study of chain-length and stereochemical dependence

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Abstract—A series of ω-alkoxy ethers were prepared with variation of the length of the aliphatic chain of suberoylanilide hydroxamic acid (SAHA, vorinostat). Eight carbon long chain analogues showed the best activity, among which several substituted benzyl ether derivatives exhibited inhibitory activity on HDAC comparable to SAHA, and antiproliferative activity on three human cell lines (NB4, H460, and HCT-116) better than SAHA. However, no significant difference in antiproliferative activity was observed between two enantiomers bearing the benzyl ether moiety.

Metalloproteases are a superfamily of ubiquitous zinc-dependent enzymes involved in a host of physiologically important processes.[1] Among two of the recently most relevant enzymes are matrix metalloproteinases (MMPs)[2] and histone deacetylases (HDACs).[3] In either case the most effective known inhibitors are hydroxamic acids that bind a zinc atom in the respective enzymes.[4]

HDACs are nuclear enzymes that play a major role in regulating gene expression. They catalyze the deacetylation of the *N*-acetyl lysine residues thereby changing the accessibility of transcription factors to DNA, and consequently affecting the chromatin remodeling process. Cell specific patterns of gene expression depending on histone acetylation result from a balance of the competing activities of two classes of enzymes, the histone acetyl transferases (HATs)[5] and the histone deacetylases (HDACs). Perturbations of this balance have been linked to cancer, and inhibition of HDAC has been shown to have antiproliferative effects on tumor cell lines, resulting in considerable interest in this field.[3,6]

The list of known inhibitors of HDACs covers a wide cross-section of structures including natural products such as trichostatin A (TSA),[7] and unnatural surrogates such as the recently launched suberoylanilide hydroxamic acid (SAHA)[8] under the name vorinostat (Fig. 1). A large body of work has been devoted to the synthesis of hydroxamic acid analogues of acyclic and heterocyclic compounds.[6]

Fragments of natural products such as amamistatins A and B (Fig. 2), containing an *N*-formyl-*N*-hydroxy lysine moiety, have been reported as HDAC inhibitors.[9]

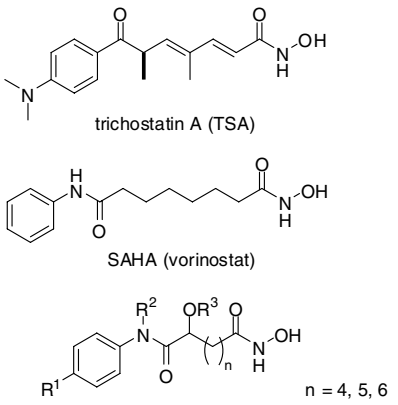

Figure 1. Structures of known HDAC inhibitors and a proposed prototype.

Keywords: Hydroxamic acid; HDAC; Anticancer activity.
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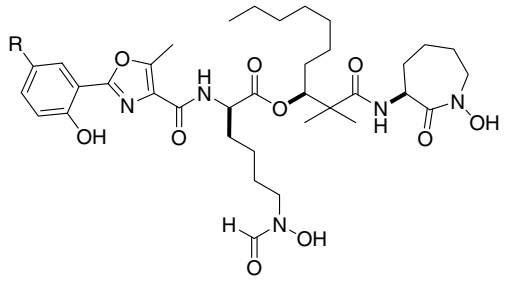
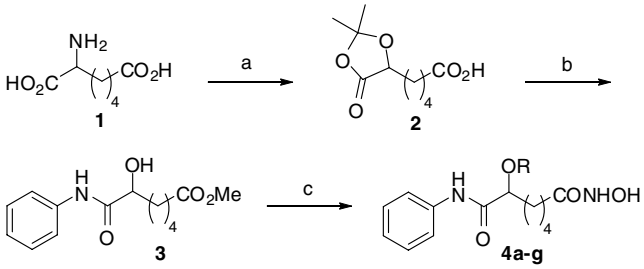


Figure 2. Structures of amamistatin A and B.

De novo design and library approaches have also been used in the search for novel HDAC inhibitors.[10]

The structural simplicity of SAHA as an effective inhibitor of HDACs has instigated the synthesis of closely related analogues. In a recent patent[11] Breslow and coworkers have reported a series of 7-substituted amide derivatives of SAHA with excellent inhibitory activities. Although alkoxy analogues of SAHA are mentioned in this patent, little if any detail on their inhibitory activity is available.[11] Efforts in the same general direction were also ongoing in our laboratory, specifically to probe the influence of the chain length of SAHA analogues possessing ω-alkoxy substituents on enzyme binding and inhibition.[12] A prototypical analogue is shown as a generic structure in Figure 1.

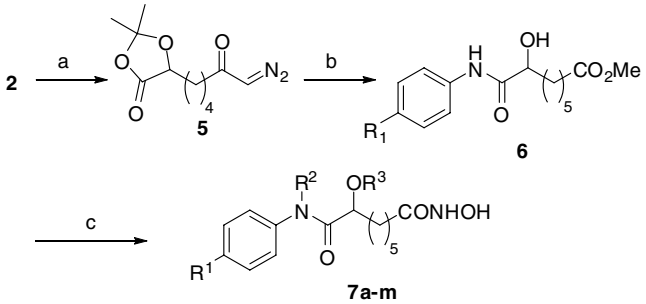
We first focused on SAHA analogues having a seven carbon chain length and featuring a series of 6-alkoxy substituents as shown in Scheme 1. Thus, racemic aminopimelic acid **1** was subjected to diazotization[13] and the resulting alcohol was protected as the lactone acetal **2**. After esterification as a methyl ester and cleavage of the acetonide protection, the resulting α-hydroxy acid was efficiently converted to anilide **3** by reaction with *N*-sulfinylaniline.[14] Alkylation with a variety of alkyl halides, followed by treatment of the resulting 6-alkoxy esters with hydroxylamine in methanolic NaOH, led to the corresponding hydroxamic acids **4b**–**g**. The most effective base for the alkylations was found to be Ag_2O, although some yields were only modest.[15] Treatment of **3** under the same conditions gave racemic 6-hydroxy pimeloylanilide hydroxamic acid (**4a**).



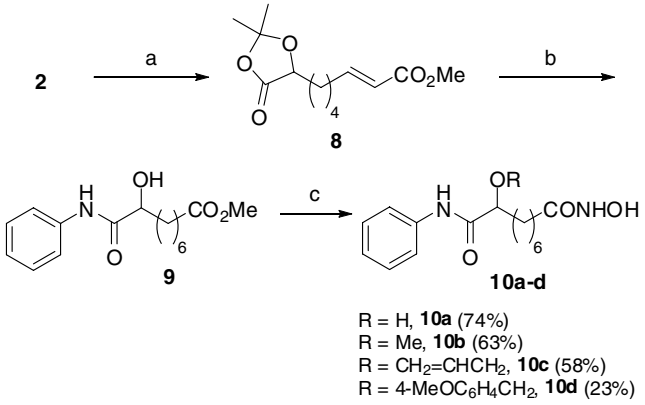
Scheme 1. Seven carbon long chain ω-alkoxy SAHA analogues **4a**–**g**. Reagents and conditions: (a) (i) $NaNO_2$, 2 N HCl, 0 °C to rt; (ii) 2,2-DMP, PTSA (72%, two steps); (b) (i) CH_2N_2, Et_2O, 0 °C to rt (99%); (ii) 70% aq AcOH, 60 °C (85%); $C_6H_5N{=}S{=}O$, 1,2,4-triazole, DCM, 0 °C to rt (84%). (c) (i) RBr or RI, Ag_2O, DMF or MeCN, rt or 40 °C (30–80%); (ii) 50% aq $HONH_2$, 1.0 N NaOH, MeOH, 0 °C to rt (75–98%).

Analogues maintaining the original SAHA chain length were prepared as shown in Scheme 2. Thus, using the common intermediate **2**, an Arndt–Eistert extension[16] via the α-diazoketone **5**, and subsequent manipulation gave anilide **6** in excellent overall yield. Similar alkylations and subsequent treatment with hydroxylamine as depicted in Scheme 1 led to the 7-alkoxy SAHA–hydroxamic acids **7a**–**m**, albeit in modest yields with the exception of the methyl and allyl ethers **7b** and **7c**. The reason for these modest yields of alkylation is not clear.[15] In one example, the *O*,*N*-bis 3-methoxybenzyl analogue **7i** was prepared along with the mono-alkylated analogue **7h**.

The last series of inhibitors included nine carbon chain analogues prepared from the common precursor **2** (Scheme 3). Thus, conversion to the aldehyde and olefin extension led to the α,β-unsaturated ester **8**. Reduction of the double bond, followed by cleavage of the acetal and anilide formation, gave **9** in excellent overall yield.



Scheme 2. Eight carbon long chain ω-alkoxy SAHA analogues **7a**–**m**. Reagents and conditions: (a) (i) $SOCl_2$, cat. DMF, CH_2Cl_2, −10 °C to rt; (ii) CH_2N_2, Et_2O, −5 °C to rt (86%, two steps); (b) (i) AgOBz, Et_3N, MeOH, −25 °C to rt (99%); (ii) 70% aq AcOH, 60 °C (98%); (iii) $R^1C_6H_4N{=}S{=}O$, 1,2,4-triazole, CH_2Cl_2, 0 °C to rt (R^1 = H, 84%; R^1 = OMe, 71%); (c) (i) R^2Br or R^2I, Ag_2O, DMF or MeCN, rt or 40 °C (25–80%); for R^2 = 4-$MeOC_6H_4CH_2$, 4-$MeOC_6H_4$-$CH_2O(C{=}NH)CCl_3$, cat. $BF_3 \cdot OEt_2$, CH_2Cl_2 (39%); (ii) 50% aq $HONH_2$, 1.0 N NaOH, MeOH, 0 °C to rt (75–99%).

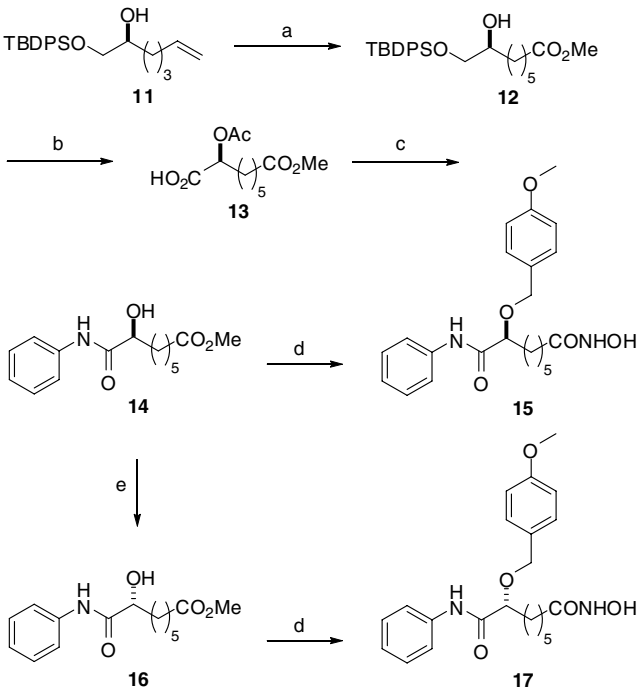


Scheme 3. Nine carbon long chain ω-alkoxy SAHA analogues **10a–d**. Reagents and conditions: (a) (i) $BH_3 \cdot DMS$, THF, 0 °C to rt (87%); (ii) $(COCl)_2$, DMSO, DCM, −78 °C, then Et_3N, −78 °C to rt (98%); (iii) $Ph_3P{=}CHCO_2Me$, CH_2Cl_2 (96%); (b) (i) $NaBH_4$, $NiCl_2 \cdot 6H_2O$, MeOH, 0 °C to rt (98%); (ii) 70% aq AcOH, 60 °C (94%); (iii) PhN=S=O, 1,2,4-triazole, DCM, 0 °C to rt (96%); (c) (i) RBr or RI, Ag_2O, DMF or MeCN, rt or 40 °C (31–74%); (ii) 50% aq $HONH_2$, 1.0 N NaOH, MeOH, 0 °C to rt (75–85%).

Alkylation and treatment with hydroxylamine led to the three 8-alkoxy and 8-hydroxy homo-SAHA analogues **10a–d**.

In order to probe the effect of chirality of the inhibitory activity of the original 6-alkoxy SAHA derivatives, we chose the *p*-methoxybenzyl ether as a prototype based on preliminary promising data on the racemate (Scheme 4). Cross metathesis of the known enantiomerically pure alkenol **11**[17] with methyl acrylate in the presence of Grubbs second generation catalyst,[18] followed by catalytic hydrogenation, gave **12** in excellent overall yield. After acetylation of the alcohol function, cleavage of the TBDPS ether, oxidation,[19] anilide formation, and deacetylation with KCN in MeOH[20] gave **14**, which was alkylated, and the product treated with hydroxylamine to give the 7-(*S*)-ether analogue **15**. Mitsunobu reaction[21] of **14** followed by etherification of the resulting **16**, and treatment with hydroxylamine gave the epimeric 7-(*R*)-ether **17**.

The pharmacological activities of the ω-alkoxy SAHA derivatives were investigated by measuring their potency to inhibit HeLa immuno-purified HDAC-2 enzyme as well as evaluating their antiproliferative activity on three human tumor cell lines (NB4, H460, and HCT-116). According to the literature data, a remarkable role in HDAC-2 inhibition and antiproliferative activity was played by the spacer group length in SAHA.[6f] In the ω-alkoxy series reported in the present study, the preferred chain length was found to be with $CH_2 = 5$ (Table 1). Among the eight carbon long chain ω-ethers, the benzyloxy derivatives **7d**, **15**, **17**, **7e–h**, and **7j** exhibited HDAC-2 inhibitory activity comparable to SAHA, but they had superior antiproliferative activity. Interestingly, no significant difference in inhibitory activity was found between the racemic *O*-(*p*-OMe) benzyl analogue **7d** and the single enantiomers (*S*-isomer, **15**, or *R*-isomer, **17**). Simple alkyl ethers or ω-hydroxy analogues **7a–c**, **7k–m** (Table 1), **4a**, **4c–d**, **4g**, **10a–b**, **10d** (see Supporting Information) were inactive against HDAC-2 at concentrations below 0.1 μM and they showed scarce to moderate cytotoxicity, with the exception of the nine carbon long ω-*O*-allyl analogue **10c** (Table 1) which exhibited HDAC-2 and tumor growth inhibitory activity similar to SAHA. On the other hand, the seven carbon chain analogues **4b**, **4e–f**, and **7i** (Table 1) were endowed with moderate HDAC-2 inhibitory activity but low antiproliferative potency. Taking into account that several factors could be involved, it is possible that HDAC-2 isoenzyme plays a marginal role in the growth of the cell lines.



Scheme 4. Enantiopure eight carbon long chain ω-(*p*-methoxy)benzyloxy SAHA analogues **15** and **17**. Reagents and conditions: (a) (i) $CH_2{=}CHCO_2Me$, Grubbs 2nd gen. catalyst, CH_2Cl_2 (95%); (ii) H_2, 10% Pd–C, MeOH (86%); (b) (i) Ac_2O, Py, DMAP (98%); (ii) TBAF-AcOH, THF, 0 °C to rt (97%); (iii) TCCA, TEMPO, $NaHCO_3$, NaBr, acetone–H_2O, 0 °C to rt (99%); (c) (i) $PhNH_2$, EDCI, HOBt, DIEA, CH_2Cl_2, 0 °C to rt (70%); (iv) KCN, MeOH, 0 °C to rt (99%); (d) (i) 4-$MeOC_6H_4O(CH{=}NH)CCl_3$, $BF_3 \cdot OEt_2$, CH_2Cl_2 (39%); (ii) 50% aq $HONH_2$, 1.0 N NaOH, MeOH, 0 °C to rt (99%); (e) (i) DIEA, Ph_3P, 4-NO_2BzOH, toluene, 0 °C to rt (83%); (ii) KCN, MeOH, 0 °C to rt (99%).

In conclusion, we have synthesized a series of ω-alkoxy analogues of SAHA and determined their inhibitory activity on HDAC-2 as well as their cytotoxic activity on three cancer cell lines. The ω-benzyloxy analogues of SAHA **7d**, **15**, **17**, **7e–h**, and **7j** were more cytotoxic and had a similar HDAC-2 inhibitor activity as compared to SAHA. The racemic *p*-methoxybenzyl ether analogue **7d** showed the same biological profile as that of the single enantiomers **15** and **17**. Thus, in spite of the very promising cytotoxic activity no stereochemical preference was found in this series. Further work that exploits the placement of hydrophobic ether appendage on the original SAHA molecule is in progress.

Table 1. In vitro inhibitory activity against HDAC-2 and cytotoxic activity of representative ω-alkoxy SAHA analogues

	HDAC-2 IC_{50} (μM) (range)		Growth inhibition IC_{50} (μM)		
	0.5–0.1	⩾0.05	NB4	H460	HCT-116
SAHA	–	+	0.70	3.40	1.20
4b	+	–	3.50	5.70	5.00
4e	+	–	4.10	10.40	8.50
4f	+	–	>5	5.50	2.40
7a	+	–	0.34	0.46	1.09
7b	+	–	0.52	1.20	0.88
7c	+	–	0.45	1.79	0.99
7d	–	+	0.12	0.52	0.22
15	–	+	0.11	0.45	0.25
17	–	+	0.07	0.50	0.39
7e	–	+	0.17	0.48	0.43
7f	–	+	0.06	0.49	0.28
7g	–	+	0.12	0.59	0.27
7h	–	+	0.16	0.59	0.63
7i	+	–	4.00	7.40	7.50
7j	–	+	0.05	0.45	0.30
7k	+	–	0.23	0.68	0.67
7l	+	–	0.25	1.00	0.50
7m	+	–	0.15	0.30	0.34
10c	–	+	0.62	1.80	0.95

Values are means of a minimum of three experiments. HDAC-2 enzyme was obtained from HeLa cell lysate. Growth inhibition was measured by SRB (sulforhodamine B) assay. See Supporting Information.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2007.09.014.

References and notes

1. For excellent reviews, see: (a) Gupta, S. P. *Chem. Rev.* **2007**, *107*, 3042; (b) Auld, D. S. In *Encyclopedia of Biological Chemistry*; Lennarz, W., Lane, M. D., Eds.; Academic Press, 2004; Vol. 1, p 652; (c) Leung, D.; Abbenante, G.; Fairlie, D. P. *J. Med. Chem.* **2000**, *43*, 305; (d) Nigel, M.; Hooper, N. M. *FEBS Lett.* **1994**, *354*, 1.
2. For reviews, see: (a) Maskos, K. *Biochimie* **2005**, *87*, 249; (b) Lopez-Otín, C.; Overall, C. M. *Nat. Rev. Mol. Cell Biol.* **2002**, *3*, 509.
3. For recent reviews on HDAC biology, see: (a) Somoza, J. R.; Skene, R. J.; Katz, B. A.; Mol, C.; Ho, J. D.; Jennings, A. J.; Luong, C.; Arvai, A.; Buggy, J. J.; Chi, E.; Tang, J.; Sang, B.-C.; Verner, E.; Wynands, R.; Leahy, E. M.; Dougan, D. R.; Snell, G.; Navre, M.; Knuth, M. W.; Swanson, R. V.; McRee, D. E.; Tari, L. W. *Strucure* **2004**, *12*, 1325; (b) Grozinger, C. M.; Schreiber, S. L. *Chem. Biol.* **2002**, *9*, 3; (c) Khochbin, S.; Verdel, A.; Lemercier, C.; Seigneurin-Berny, D. *Curr. Opin. Genet. Dev.* **2001**, *11*, 162; (d) Wu, J.; Grunstein, M. *Trends Biochem. Sci.* **2005**, *25*, 619; (e) Archer, S. Y.; Hodin, R. A. *Curr. Opin. Genet. Dev.* **1999**, *9*, 171.
4. (a) Yang, K.; Lou, B. *Mini-Rev. Med. Chem.* **2003**, *3*, 349; (b) Muri, E. M. F.; Nieto, M. I.; Sindelar, R. D.; Williamson, J. D. *Curr. Med. Chem.* **2002**, *9*, 1631; See also: (c) Suzuki, T.; Miyata, N. *Curr. Med. Chem.* **2005**, *12*, 2867, and references therein; (d) Hanessian, S.; Vinci, V.; Auzzas, L.; Marzi, M.; Giannini, G. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 4784.
5. (a) Iizuka, M.; Smith, M. M. *Curr. Opin. Genet. Dev.* **2003**, *13*, 154; (b) Roth, S. Y.; Denu, J. M.; Allis, C. D. *Annu. Rev. Biochem.* **2001**, *70*, 81.
6. For recent reviews on HDAC inhibitors, see: (a) Rodriguez, M.; Aquino, M.; Bruno, I.; De Martino, G.; Taddei, M.; Gomez-Paloma, L. *Curr. Med. Chem.* **2006**, *13*, 1119; (b) Golden, J. E.; Pearl, M. J.; Johnstone, R. W. *Nat. Rev. Drug Disc.* **2006**, *5*, 769; (c) Minucci, S.; Pelicci, P. G. *Nat. Rev. Cancer* **2006**, *6*, 38; (d) Moradei, O.; Maroun, C. R.; Paquin, I.; Vaisburg, A. *Curr. Med. Chem. Anti-Canc. Agents* **2005**, *5*, 529; (e) Mai, A.; Massa, S.; Rotili, D.; Cerbara, I.; Valente, S.; Pezzi, R.; Simeoni, S.; Ragno, R. *Med. Res. Rev.* **2005**, *25*, 261; (f) Monneret, C. *Eur. J. Med. Chem.* **2005**, *40*, 1; (g) Dokmanovic, M.; Marks, P. A. *J. Cell. Biochem.* **2005**, *96*, 293; (h) Vanhaecke, T.; Papeleu, P.; Elaut, G.; Rogiers, V. *Curr. Med. Chem.* **2004**, *11*, 1629; (i) Villar-Garea, A.; Esteller, M. *Int. J. Cancer* **2004**, *112*, 171; (j) Miller, T. A.; Witter, J.; Belvedere, S. *J. Med. Chem.* **2003**, *46*, 5097; (k) Arts, J.; Schepper, S.; Van Emelen, K. *Curr. Med. Chem.* **2003**, *10*, 2343; (l) Johnstone, R. W. *Nat. Rev. Drug Disc.* **2002**, *1*, 287; See also: (m) Finnin, M. S.; Donigian, J. R.; Cohen, A.; Richon, V. M.; Rifkind, R. A.; Marks, P. A.; Breslow, R.; Pavletich, N. P. *Nature* **1999**, *401*, 188; (n) Wang, D.-F.; Wiest, O.; Helquist, P.; Lan-Hargest, H.-Y.; Wiech, N. L. *J. Med. Chem.* **2004**, *47*, 3409.
7. Isolation and activity: (a) Tsuji, N.; Kobayashi, M.; Nagashima, K.; Wakisaka, Y.; Koizumi, K. *J. Antibiot.* **1976**, *29*, 1; (b) Yoshida, M.; Kijima, M.; Akita, M.; Beppu, T. *J. Biol. Chem.* **1990**, *265*, 17174; Synthesis: (c) Mori, K.; Koseki, K. *Tetrahedron* **1998**, *44*, 6013.
8. (a) Grant, S.; Easley, C.; Kirkpatrick, P. *Nat. Rev. Drug Disc.* **2007**, *6*, 21; (b) Gediya, L. K.; Pankaj Chopra, P.; Purushottamachar, P.; Maheshwari, N.; Njar, V. C. O. *J. Med. Chem.* **2005**, *48*, 5047; (c) Huang, L.; Pardee, A. B. *Mol. Med.* **2000**, *6*, 849; (d) Butler, L. M.; Agus, D. B.; Scher, H. I.; Higgins, B.; Rose, A.; Cordon-Cardo, C.; Thaler, H. T.; Rifkind, R. A.; Marks, P.; Richon, V. M. *Cancer Res.* **2000**, *60*, 5165; (e) Richon, V. M.; Emiliani, S.; Verdin, E.; Webb, Y.; Breslow, R.; Rifkind, R. A.; Marks, P. A. *Proc. Natl. Acad. Sci. U.S.A.* **1998**, *95*, 3003.
9. Fennell, K. A.; Miller, M. J. *Org. Lett.* **2007**, *9*, 1683.
10. See for example: (a) Siliphaivanh, P.; Harrington, P.; Witter, D. J.; Otte, K.; Tempest, P.; Kattar, S.; Kral, A. M.; Fleming, J. C.; Deshmukh, S. V.; Harsch, A.; Secrist, P. J.; Miller, T. A. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 4619; (b) Liu, T.; Kapustin, G.; Etzkorn, F. A. *J. Med. Chem.* **2007**, *50*, 2003; (c) Remiszewski, S. W.; Sambucetti, L. C.; Bair, K. W.; Bontempo, J.; Cesarz, D.; Chandramouli, N.; Chen, R.; Cornell-Kennon, S.; Dean, K.; Diamantidis, G.; France, D.; Green, M. A.; Howell, K. L.; Kashi, R.; Kwon, P.; Lassota, P.; Martin, M. S.; Mou, Y.; Perez, L. B.; Sharma, S.; Smith, T.; Sorensen, E.; Taplin, F.; Trogani, N.; Versace, R.; Walker, H.; Weltcher-Engler, S.; Wu, A.; Atadja, P. *J. Med. Chem.* **2003**, *46*, 4609.
11. (a) Breslow, R.; Belvedere, S.; Gershell, L.; Miller, T. A.; Marks, P. A.; Richon, V. M.; Rifkind, R. U.S. Patent 6,511,990-B1, **2003**; (b) Richon, V.; Marks, P. A.; Rifkind, R. A.; Breslow, R.; Belvedere, S.; Gershell, L.; Miller, T.

A. WO0118171-A2, **2001**; (c) Breslow, R.; Pavletich, N. P. *Nature* **1999**, *401*, 188.
12. Hanessian, S.; Auzzas, L.; Giannini, G.; Vesci, L.; Pisano, C. Eur. Pat. Appl. No. 07104071.1, **2007**.
13. Brewster, P.; Hiron, F.; Huges, E. D.; Ingold, C. K.; Rao, P. A. D. S. *Nature (London)* **1950**, *166*, 179.
14. (a) Chidambaram, R.; Zhu, J.; Penmetsa, K.; Kronenthal, D.; Kant, J. *Tetrahedron Lett.* **2000**, *41*, 6017; (b) Shin, J. M.; Kim, Y. H. *Tetrahedron Lett.* **1986**, *27*, 1921; (c) Kim, Y. H.; Shin, J. M. *Tetrahedron Lett.* **1985**, *26*, 3821.
15. The following conditions resulted mostly in decomposition: (a) NaH/THF or DMF, TBAI; (b) KH/THF or DMF, TBAI; (c) KHMDS/THF. In Ag_2O-mediated alkylations, the starting material was usually recovered after 6–12 h reaction.
16. (a) Toyooka, N.; Okomura, M.; Nemoto, H. *J. Org. Chem.* **2002**, *67*, 6078; Leading references: (b) Bachman, W. E.; Struve, W. S.. In *Org. React.*; John Wiley and Sons, Inc.: New York, N.Y., 1942; 1, p. 38; (c) Newman, M. S.; Beal, P. F., III *J. Am. Chem. Soc.* **1950**, *72*, 5163.
17. Tate, E. W.; Dixon, D. J.; Ley, S. V. *Org. Biomol. Chem.* **2006**, *4*, 1698.
18. (a) Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360; (b) Connon, S. J.; Blechert, S. *Angew. Chem. Int. Ed.* **2003**, *42*, 1900.
19. De Luca, L.; Giacomelli, G.; Masala, S.; Porcheddu, A. *J. Org. Chem.* **2003**, *68*, 4999.
20. (a) Hanessian, S.; Kagotani, M. *Carbohydr. Res.* **1990**, *202*, 67; (b) Herzig, J. *J. Org. Chem.* **1986**, *51*, 727.
21. Mitsunobu, O. *Synthesis* **1981**, 1.