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$Al(OTf)_3$-Mediated Epoxide Ring-Opening Reactions: Toward Piperazine-Derived Physiologically Active Products

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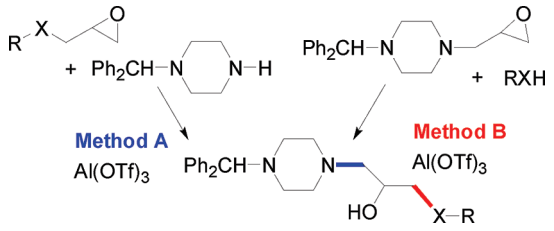

$Al(OTf)_3$ is a good catalyst for the ring opening of epoxides, forming β-amino alcohols bearing the piperazine motif. Two different strategies were examined, where the glycidyl ether resided on one-half of the molecule or the other, allowing insight into a best-case approach for the ring-opening step. Each half of the molecule contained an heteroatom that could be used either to attach the glycidyl moiety or as the nucleophile in the ring-opening reaction, for the same set of reagents, allowing this approach.

1,2-Amino alcohols represent an important class of organic molecules. They have found application in medicinal chemistry,[1] organic synthesis in general, and particularly in asymmetric synthesis as chiral ligands and auxiliaries.[2] These molecules are usually prepared by reacting an epoxide at elevated temperatures in the presence of an excess of an amine.[3] Alternatively, a preformed halohydrin can be reacted with an amine in the presence of a stoichiometric amount of a base.[4a−d] The apparent disadvantage of this method is the generation of undesired hydrohalous acid, which has to be neutralized with an equimolar amount of base, generating significant amounts of salts in the process and rendering the separation of water-soluble amino alcohols from the salts nontrivial. In organic-soluble amino alcohols the purification is not particularly onerous, but salt byproduct are generated nevertheless.

Piperazine-based β-amino alcohols are known for their biological activity. They find applications as positive inotropic agents, increasing myocardial contractivity, in the treatment of cardiac disorders such as congestive heart failure.[5−8] Examples include Carsatrin[5] and DPI201-106[6] (**1** and **2**, Figure 1). A notable β-amino alcohol is propranolol (**3**, Figure 1), one of the first non-selective β-blockers developed finding widespread use in the treatment of hypertension. They have also found applications as Ca^{2+} antagonists[4a−d] and dopamine uptake inhibitors.[4a−d] The quinoline-based β-amino alcohols similar to **4** bearing the piperazine motif (Figure 1) have even found application in the reversal of multidrug resistance in cancer cells.[9] Piperazine **4** showed activity four times higher than Verapamil, a calcium channel blocking drug that is known to reverse multidrug resistance in cancerous cells.[9]

In all cases the synthesis included the reaction of a chlorohydrin with a nucleophile in the presence of stoichiometric amounts of base or by the ring opening of an epoxide, where the epoxide was heated in the presence of the nucleophile.[4a−d,5−9] Obvious advantages of using an epoxide as a substrate in the generation of 1,2-amino alcohols are the general atom efficiency of the reaction.

Previous work performed in our laboratories reported the use of $Al(OTf)_3$ as an efficient Lewis acid catalyst for the ring opening of epoxides by various alcohols as well as by aliphatic and aromatic amines (Scheme 1).[10] The aminolysis reaction was found to be regioselective for nucleophilic attack at the less hindered carbon atom of the epoxide ring, a feature of S_N2-type reaction mechanisms as opposed to a borderline S_N2-type mechanism, which may favor attack at the more hindered carbon center.[10] Catalyst reuse was also accomplished by simple extraction of the catalyst with water, once the reaction had been completed, and subsequently removing the water under reduced pressure and elevated temperatures. The catalyst was found to retain its activity through three cycles. Other Lewis acids reported to be active toward the ring opening of epoxides include $Ti(O^iPr)_4$,[11]

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(10) (a) Williams, D. B. G.; Lawton, M. *Tetrahedron Lett.* **2006**, *47*, 6557–6560. (b) Williams, D. B. G.; Lawton, M. *Org. Biomol. Chem.* **2005**, *3*, 3269–3272.
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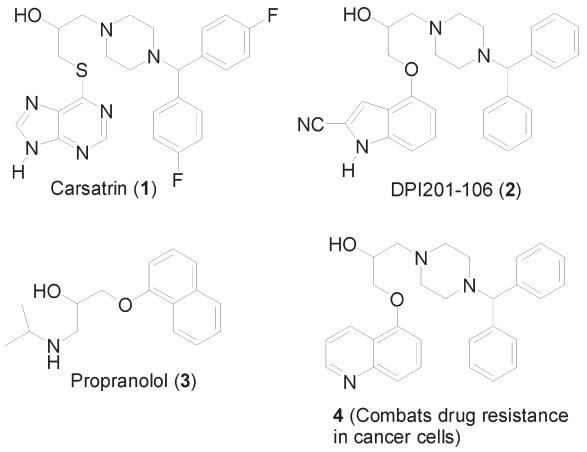
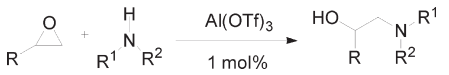


FIGURE 1. Biologically active piperazine-based compounds.

SCHEME 1. Aminolysis of Epoxides Using Al(OTf)$_3$



$TaCl_5$,[12] Bi salts,[13] $ZrCl_4$,[14] $Sm(OTf)_3$,[15] $CoCl_2$,[16] $CuBF_4$,[17] $ZnCl_2$,[18] and $Sc(OTf)_3$.[5]

The present work describes and compares two epoxide ring-opening approaches to β-amino alcohols containing piperazine moieties. In the first, the N−C bond (Figure 2, bond a) is formed in the ring-opening reaction, whereas in the second the C−X bond (X = O, S, N, Figure 2, bond b) is formed by this step. In both cases, $Al(OTf)_3$ is used as a catalyst for the key bond-forming step.

Synthesis of Glycidyl Derivatives. The *S*-glycidyl ether substrates (Scheme 2) were prepared according to a literature procedure.[19] Reaction of the thiol with epichlorohydrin in the presence of KOH as base in a biphasic 1,4-dioxane/water mixture yielded the desired *S*-glycidyl ether in good yields.

The *O*-glycidyl aryl ether substrates **6a**−**6c** (Figure 3) are commercially available but can be prepared according to a literature method,[20] whereby the phenol is dissolved in epichlorohydrin and stirred in the presence of K_2CO_3 and a phase transfer catalyst (n-Bu_4NBr) to give the desired products. Application of this method to *l*-menthol resulted only in low yields (<20%) of the corresponding glycidyl ether. However, a modification of a two-step protocol set out in a patent[21] led to significant improvements being realized

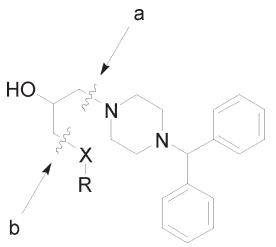
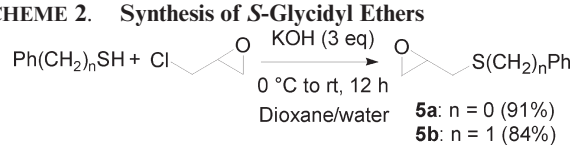


FIGURE 2. Key bond disconnections for target β-amino alcohols.

SCHEME 2. Synthesis of *S*-Glycidyl Ethers



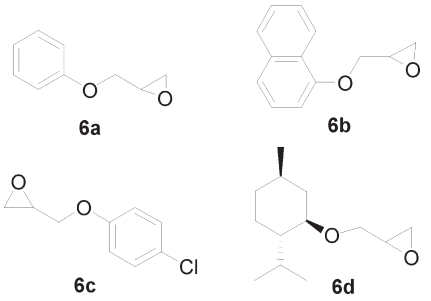
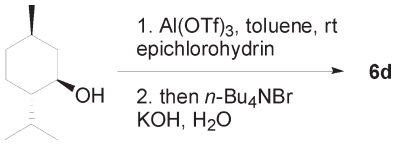


FIGURE 3. *O*-Glycidyl ethers.

SCHEME 3. Synthesis of *O*-Glycidyl Ethers



(40% over two steps, Scheme 3). Here, $Al(OTf)_3$-catalyzed chlorohydrin formation followed by base-promoted cyclization led to the desired glycidyl ether **6d**. The $Al(OTf)_3$ used as catalyst could be readily recycled by simple extraction with water and drying the aqueous layer under vacuum with heating.[22] In this way, the catalyst could be recycled four times with no loss of activity (the yield of 40% cited is the average of four runs, using recycled catalyst in the last three runs).

When preparing the glycidyl *amines*, some problems were encountered. Synthesis of compound **7a** was initially accomplished through a method similar to that used for synthesis of the *S*-glycidyl ethers,[19] with the main variation being the use of acetonitrile as solvent instead of 1,4-dioxane. However, upon extension of this methodology to the aromatic amines (Table 1, see entries 2−6 for the structures of the desired compounds), low yields and mixed reaction products were encountered with quaternization of the amine being a serious issue. In an attempt to overcome this problem, a two-step approach was adopted whereby epichlorohydrin was ring-opened by the desired amine in an $Al(OTf)_3$-catalyzed reaction to give the

(12) Chandrasekhar, S.; Ramachandar, T.; Prakash, S. J. *Synthesis* **2000**, 1817–1818.
(13) Chakraborti, A. K.; Kondaskar, A. *Tetrahehron Lett.* **2003**, *44*, 8315–8317.
(14) Yadav, J. S.; Reddy, A. R.; Narsaiah, A. V.; Reddy, B. V. S. *J. Mol. Catal. A: Chem.* **2007**, *261*, 207–212.
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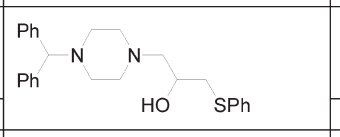
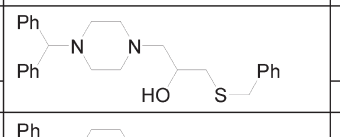
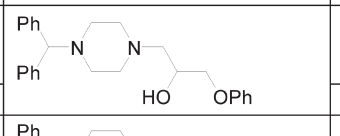
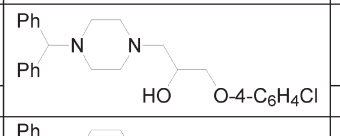
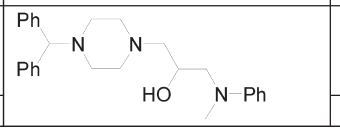
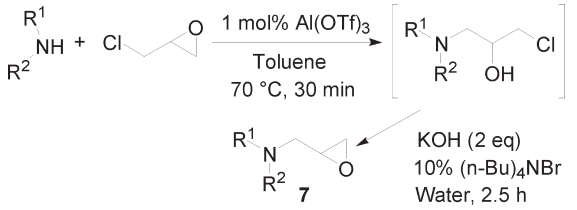
(22) The catalyst was recycled by extracting the organic phase with water (3 × 2 mL), removing the water under vacuum by heating to 80 °C, and drying under high vacuum at 140 °C. Final drying may also be effected at 120 °C under a flow of dry nitrogen.

TABLE 1. Yields of *N*-Glycidyl Amines for the Two-Step Process

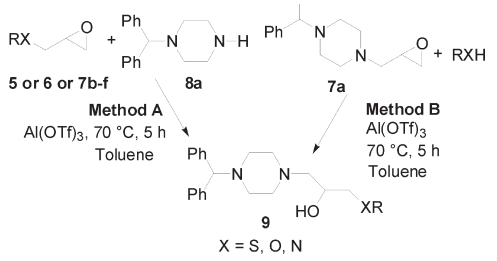
Entry	Product	Method	Yield (%)
1[a]		A	**9a**: 82
2[a]		B	**9a**: 48
3[a]		A	**9b**: 86
4[a]		B	**9b**: 30
5[b]		A	**9c**: 73
6[b]		B	**9c**: 0
7[b]		A	**9d**: 85
8[b]		B	**9d**: 0
9[b]		A	**9e**: 78
10[b]		B	**9e**: 33

[a]5 mol % $Al(OTf)_3$ catalyst. [b]1 mol % $Al(OTf)_3$ catalyst.

SCHEME 4. Synthesis of *N*-Glycidyl Amines



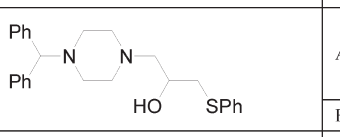
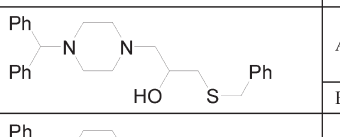
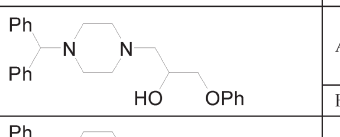
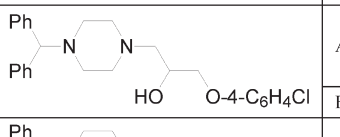
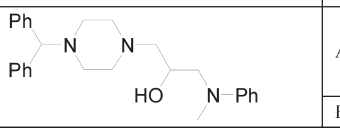
SCHEME 5. Approaches for Obtaining β-Amino Alcohols



intermediate halohydrin, which was subsequently dehydrohalogenated with an aqueous base to yield the desired *N*-glycidyl amine, in a one-pot process (Scheme 4). The use of $Al(Otf)_3$ as a catalyst for the aminolysis of epoxides has recently been reported.[10] This method yielded the desired *N*-glycidyl amines in moderate to excellent yields (Table 1) after two steps. The two-step process was found to be a significant improvement on the direct one-step KOH-mediated glycidyl amine formation for aromatic amines.

Epoxide Aminolysis Method Evaluation. Two different approaches for obtaining the desired β-amino alcohol were examined (Scheme 5). The first involved reaction of the glycidyl ether or amine with a piperazine-based amine nucleophile (Scheme 5, Method A). The second involved the reaction of an heteroatom nucleophile with a preformed piperazine-based glycidyl amine (Scheme 5, Method B).

TABLE 2. Comparison of Methods A and B for Obtaining β-Amino Alcohols

Entry	Product	Method	Yield (%)
1[a]		A	**9a**: 82
2[a]		B	**9a**: 48
3[a]		A	**9b**: 86
4[a]		B	**9b**: 30
5[b]		A	**9c**: 73
6[b]		B	**9c**: 0
7[b]		A	**9d**: 85
8[b]		B	**9d**: 0
9[b]		A	**9e**: 78
10[b]		B	**9e**: 33

[a]10 mol % $Al(OTf)_3$ catalyst. [b]5 mol % $Al(OTf)_3$ catalyst.

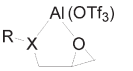


FIGURE 4. Proposed metal chelate structure of aluminum catalyst and heteroatom glycidyl ether.

Inspection of the comparative results detailed in Table 2 reveals that use of a piperazine-based amine to ring-open an heteroatom glycidyl ether (Method A) is the favored method for the preparation of the desired β-amino alcohols. The improved activity of the catalyst under these conditions may be rationalized by invoking the formation of a deactivated metal-glycidyl epoxide chelate species (Figure 4). Here, the positive charge that is transferred to the α-carbon of the oxirane is diminished by chelation of the heteroatom of the glycidyl ether to the aluminum ion, as has been previously suggested.[10] This effect is pronounced with glycidyl ethers bearing a more strongly basic (harder Lewis base) heteroatom functionality. In the case of entries 1−4 in Table 2 where sulfur is the heteroatom, the *N*-glycidyl ether bearing a basic nitrogen (Table 2, entries 2 and 4) would significantly deactivate the catalyst in the intermediate chelated state compared to the analogous the *S*-glycidyl ethers (Table 2, entries 1 and 3). This is because of unfavorable hard−soft Lewis acid−Lewis base interactions in the latter instance, which demonstrates the hard−soft acid−base theory set forth by Pearson.[23] The difference in outcome is more pronounced when the *O*-glycidyl ethers are compared to the *N*-glycidyl ethers (Table 2, entries 5−8), and it becomes clear that Method A is superior to Method B.

The difference in the two methods employed to obtain the desired β-amino alcohols is somewhat less obvious when *N*-glycidyl amines and nitrogen nucleophiles are used (Table 2, entries 9 and 10), but Method A still dominates.

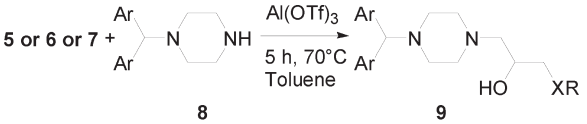
(23) Pearson, R. G.; Songstad, J. *J. Am. Chem. Soc.* **1967**, *89*, 1827–1836.

TABLE 3. Ring-Opening of Various Epoxides with Piperazine-Based Nucleophiles

entry	glycidyl substrate	8	XR	R	yield (%)
1[a]	**5a**	**8a**	SPh	H	**9a**: 82
2[a]	**5a**	**8b**	SPh	F	**9f**: 75
3[a]	**5b**	**8a**	SBn	H	**9b**: 86
4[a]	**5b**	**8b**	SBn	F	**9g**: 66
5[b]	**6a**	**8a**	OPh	H	**9c**: 73
6[b]	**6b**	**8a**	*O*-1-naphthyl	H	**9h**: 88
7[b]	**6c**	**8a**	*O*-4-C_6H_4Cl	H	**9d**: 85
8[b]	[c]	**8a**	*O*-*t*Bu	H	**9i**: 88
9[b]	[c]	**8a**	*O*-allyl	H	**9j**: 79
10[b]	**6d**	**8a**	*O*-menthyl	H	**9k**: 72
11[b]	**7b**	**8a**	N(CH_3)Ph	H	**9e**: 78
12[a]	**7c**	**8a**	NH-4-C_6H_4Cl	H	**9l**: 86
13[a]	**7d**	**8a**	NHPh	H	**9m**: 88
14[a]	**7e**	**8a**	NH-4-$C_6H_4OCH_3$	H	**9n**: 81
15[a]	**7f**	**8a**	NH-4-C_6H_4-*i*Pr	H	**9o**: 67

[a]10 mol % $Al(OTf)_3$ catalyst. [b]5 mol % $Al(OTf)_3$ catalyst. [c]Commercially available glycidyl ethers.

SCHEME 6. General Method for Obtaining Piperazine-Based β-Amino Alcohols



Ar = **8a**: C_6H_5, **8b**: 4-C_6H_4F
XR = defined in Table 3

The difference in yields that is observed can be explained by the basicity and nucleophilicity of the two types of amines used, i.e., aromatic as opposed to aliphatic amines. To elaborate, an aromatic amine with significantly reduced basicity would be best suited for use as the heteroatom functionality of the *N*-glycidyl amine, leading to a less-deactivated intermediate chelate state (Figure 4), whereas an aliphatic amine with better nucleophilicity would be best suited for use as the nucleophile.

Epoxide Aminolysis Method Application. Application of Method A (Scheme 5) to the ring opening of various epoxides bearing different heteroatom functionalities provided a range of β-amino alcohols in good yields (Scheme 6, Table 3).

The reaction to produce **9e** was scaled up and also subjected to recycling of the $Al(Otf)_3$ catalyst. When the scale was increased to 10.00 g (0.040 mol) of the piperazine substrate **8a** and 6.45 g (0.40 mol) of *N*-glycidyl ether **7b**, the average yield of three runs was 81%. The second and third runs were performed with recycled catalyst.[22]

To place these results into context, the reactions to generate sulfide products **9a**, **9b**, **9g**, and **9f** from the corresponding *S*-glycidyl ethers according to Method A were performed in the absence of catalyst, yielding the products in yields of only 3%, 13%, 9%, and 8%, respectively, under otherwise identical conditions. These results clearly exemplified the need for the catalyst.

To summarize, aluminum(III) triflate was found to be an effective recyclable catalyst for the ring opening of heteroatom-substituted glycidyl ethers to give the corresponding piperazine-based β-amino alcohols. This work establishes that the optimum approach (determined on the basis of comparisons of two synthetic directions toward the same target molecules) involves the use of the glycidyl entity attached to the less nucleophilic heteroatom while retaining the more nucleophilic heteroatom free for the ring-opening reaction (i.e., a preference for Method A over Method B, Scheme 5). This technique tolerates a range of nucleophiles that includes those bearing S, O, and N atoms and is shown to be readily scalable.

Experimental Section

Typical Procedure for the Preparation of *N*-Glycidyl Ethers. (4-Isopropyl-phenyl)-oxiranylmethyl-amine (7f). To a mixture of $Al(OTf)_3$ (0.024 g, 50 μmol) and 4-isopropyl-aniline (0.137 mL, 1 mmol) in toluene (5 mL) was added epichlorohydrin (0.081 mL, 1 mmol). The mixture was stirred at 70 °C for 30 min, after which it was cooled to room temperature and KOH (0.112 g, 20 mmol) and $(n\text{-Bu})_4NBr$ (0.032 g, 100 μmol) dissolved in water (5 mL) were added. The mixture was stirred for 2.5 h at room temperature, after which it was extracted with DCM (3 × 5 mL) and the combined organic layers washed with water (2 × 5 mL) and then dried with magnesium sulfate. The excess organic solvent was removed under reduced pressure, and the resulting residue was purified by column chromatography (silica gel, Merck Kieselgel 60 230−400 mesh, 4:1 hexane/ethyl acetate) to afford **7f** (0.115 g, 60%) as a yellow oil: TLC R_f = 0.31 (4:1 hexane/ethyl acetate); ^1H NMR (300 MHz, $CDCl_3$) δ 7.06 (d, 2H, *J* = 8.7 Hz), 6.60 (d, 2H, *J* = 8.7 Hz), 3.78 (br s, 1H), 3.51 (dd, 1H, *J* = 15.5, 4.7 Hz), 3.24−3.18 (m, 2H), 2.86−2.77 (m, 2H), 2.69 (dd, 1H, *J* = 5.1, 2.4 Hz), 1.21 (d, 6H, *J* = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.8, 138.4, 127.1, 113.0, 51.0, 45.4, 45.3, 33.1, 24.2; IR ν_{max} (ATR) 3305, 2957, 1614, 1518, 1361, 1196 cm^{-1}; ESI-MS *m*/*z* (relative intensity) 192 ($[M + H]^+$, 5), 167 (30), 149 (65), 138 (100), 117 (25), 110 (15); ESI HRMS $[M + H]^+$ calcd for $C_{12}H_{18}ON$, 192.1388; found, 192.1385.

Typical Procedure for the Ring Opening of Epoxides. 1-(4-Benzhydryl-piperazin-1-yl)-3-(4-isopropyl-phenylamino)-propan-2-ol (9o). To a mixture of **8a** (0.2 g, 0.792 mmol) and $Al(OTf)_3$ (0.038 g, 0.079 mmol) in toluene(2 mL) was added **7f** (0.151 g, 0.792 mmol). The reaction mixture was allowed to stir at 70 °C for 5 h. The reaction was then quenched by the addition of aqueous sodium bicarbonate (5 mL). The reaction mixture was extracted with DCM (3 × 5 mL), and the combined organic layers were washed with water (2 × 5 mL) and dried with magnesium sulfate. The excess organic solvent was removed under reduced pressure, and the resulting residue purified by column chromatography (silica gel, Merck Kieselgel 60 230−400 mesh, 1:1 hexane/ethyl acetate−9:1 DCM/MeOH) to afford **9o** (0.236 g, 67%) as a yellow oil: TLC R_f = 0.41 (1:1 hexane/ethyl acetate); ^1H NMR (300 MHz, $CDCl_3$) δ 7.46 (d, 4H, *J* = 7.4 Hz), 7.31 (t, 4H, *J* = 7.4 Hz), 7.24−7.19 (t, 2H, *J* = 7.4 Hz), 6.95 (d, 2H, *J* = 8.4 Hz), 6.48 (d, 2H, *J* = 8.4 Hz), 4.12 (s, 1H), 3.87−3.79 (m, 1H), 3.13 (dd, 1H, *J* = 12.4, 3.6 Hz), 2.92 (dd, 1H, *J* = 12.4, 6.5 Hz), 2.71 (sp, 1H, *J* = 6.9 Hz), 2.60−2.50 (m, 2H), 2.45−2.25 (m, 8H), 1.11 (d, 6H, *J* = 6.9 Hz); ^{13}C (75 MHz, $CDCl_3$) δ 146.3, 142.6, 138.1, 128.5, 127.8, 127.0, 126.9, 113.1, 76.1, 65.1, 61.4, 53.4, 51.9, 47.9, 33.1; IR (ATR) 3411, 2963, 2797, 1615, 1519, 1451, 1138 cm^{-1}; ESI-MS *m*/*z* (relative intensity) 444 ($[M + H]^+$, 100), 167 ($[Ph_2CH]^+$, 10); ESI HRMS $[M + H]^+$ calcd for $C_{29}H_{38}ON_3$, 444.3015; found, 444.3007

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Supporting Information Available: Analytical characterization data, ^1H and ^{13}C NMR spectra of all compounds, and reference list for known compounds. This material is available free of charge via the Internet at http://pubs.acs.org.