Zeolite β-Induced Rearrangement of Alkoxybenzyl Allyl Ethers to Aldehydes and Ketones. 5.[1] Variation of the Allylic Moiety

Johan Wennerberg, Charlotte Olofsson, and Torbjörn Frejd*

Organic Chemistry 1, Department of Chemistry, Lund University, P.O. Box 124, S-221 00 Lund, Sweden

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Allylic PMB ethers rearranged in the presence of zeolite β to form 4-arylbutanals or 5-arylpentanones depending on the substituent pattern of the allylic moiety. Best results were obtained with substrates carrying simple substituents in the allylic 2-position, but a couple of substrates lacking a 2-substituent also rearranged. More functionalized substituents in this position were not tolerated. A propargyl PMB ether and a homoallylic PMB ether rearranged as well, but the products were mixtures of isomeric olefins. The 4-arylbutanals **2c** and **2e** and the 5-arylpentanone **2j** were cyclized in PPA to give naphthalene and dihydronaphthalene derivatives, respectively.

Introduction

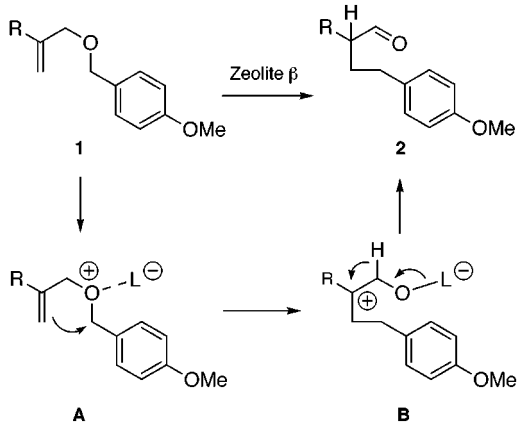
A new rearrangement to give 4-arylbutanals (**2**) was recently uncovered when certain benzyl allyl ethers (**1**) were treated with zeolite β or $BF_3{\cdot}OEt_2$. The mechanism comprises a 1,4-rearrangement of the benzylic grouping followed by, or concomitant with, a 1,2-hydride or 1,2-alkyl shift (Scheme 1).[1,2] For simplicity, we call the entire sequence the BenzAll rearrangement (benzyl allyl ether rearrangement). Among several catalysts tested, zeolite β was found to give the best results even if a few other catalysts also promoted the rearrangment.[3] We here report the results using a number of *p*-methoxybenzyl (PMB) ethers carrying various substitued allylic moieties as part of an investigation of the scope and limitations of this rearrangement.

Results and Discussion

The reactions were performed on a 1 mmol scale by treating the PMB ethers with 100 mg of zeolite β in dichloromethane for 12 h at room temperature, unless otherwise stated. Since a carbocation intermediate (**B**) may be involved in the rearrangement, it was anticipated that derivatives carrying cation-stabilizing substituents in the 2-position would be ideal substrates. On the other hand, for substrates carrying electron-withdrawing group in this position, the rearrangement was expected to be more difficult or even prevented. It should also be mentioned that the migration of the benzyl unit is mostly intramolecular, which we reported earlier by using crossover experiments.[2]

As seen in Table 1, the 2-substituted PMB ethers capable of forming a tertiary or secondary cation at the 2-position rearranged to give the corresponding aldehydes **2a**−**f** in moderate to good yields. In particular, the allylic silane **1g** was expected to be a very good substrate due to the β-silicon effect,[4,5] and we expected to obtain the allylic alcohol **2g**. Indeed, a similar case was very recently reported by Ley et al.[6] However, since only **2b** was detected (52%), compound **2g** may have been formed in situ but in that case rearranged under the influence of the zeolite. It is known that such acid-catalyzed allylic alcohol to aldehyde rearrangements are particularly facile for allylic alcohols branched at the 2-position.[7] Alternatively, protiodesilylation to **1b** could initially have taken place followed by the BenzAll rearrangement to give **2b**. Further investigations are necessary to clearify these details.

Scheme 1. Suggested Mechanism of the BenzAll Rearrangement



Despite the lack of a 2-substituent, the unsubstituted **1a** and compound **1i** rearranged efficiently. In the case of **1i**, a 2:1 mixture of ketone **2i** and aldehyde **2b** was obtained as a result of competing 1,2-hydride and 1,2-methyl shifts. This was noticed earlier for compound **1j** as well, which gave ketone **2j** and aldehyde **2k** also in a 2:1 ratio.[2] A chloro substituent in the 2-position of the allylic part should be able to delocalize the positive charge in the intermediate, thus facilitating the BenzAll rearrangement. In line with this reasoning, the chloro derivative **1h** gave α-chloro aldehyde **2h**, which, however, was unstable toward chromatographic purification and

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(5) Keck, G. E.; Castellino, S. *Tetrahedron Lett.* **1987**, *28*, 281−284.
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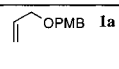
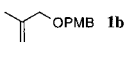
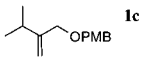
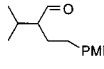
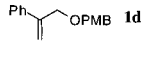
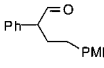
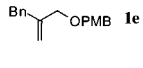
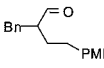
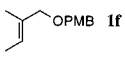
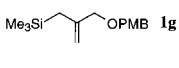
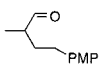
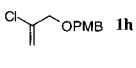
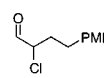
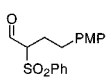
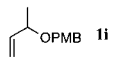
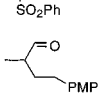
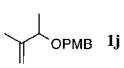
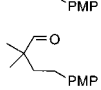
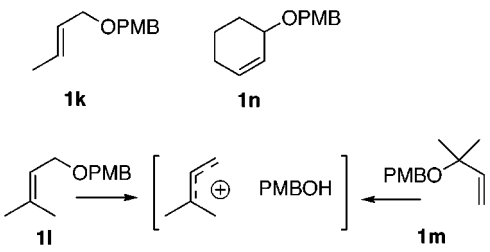
Table 1. Results of the Zeolite β-Catalyzed Rearrangement of PMB Ethers 1a−j[a]

Entry	Starting material	Product (yield %)[b]	
1	 **1a**	 **2a** (77)	
2	 **1b**	 **2b** (83)	
3	 **1c**	 **2c** (74)	
4	 **1d**	 **2d** (54)	
5	 **1e**	 **2e** (41)	
6	 **1f**	 **2f** (63)	
7	 **1g**	 **2g** not detected	 **2b** (52)
8	 **1h**	 **2h** not isolated	 **3** (53)
9	 **1i**	 **2i** (45)	 **2b** (23)
10	 **1j**	 **2j** (42)	 **2k** (25)

[a] Conditions: 1 mmol scale, 100 mg of zeolite β, 12 h, rt. [b] PMP = *p*-methoxyphenyl.

Scheme 2



therefore had to be converted into a more stable compound. As trapping agent, sodium benzenesulfinate turned out to be convenient since it was easy to handle and gave a smooth conversion of **2h** into the stable phenyl sulfone **3** at room temperature.

Despite their similar structures, PMB ethers **1k**−**n** behaved very differently (Scheme 2). While **1k** and **1n** were essentially unaffected even after prolonged reaction times and higher reaction temperatures, compounds **1l** and **1m** rapidly gave a multitude of products already at room temperature. The intramolecularity of the reaction seems to account for the reluctance of **1n** to rearrange. Here, the terminal carbon of the double bond may not come close enough to the benzyl carbon to make the 1,4-migration possible. This is clearly seen by inspection of molecular models. Also, the sluggish behavior of **1k** is possible to rationalize by the intramolecular migration of the benzylic moiety presumably as a cation or cation-like species. In this case, molecular models indicated that the methyl group of the olefinic part and the p-methoxyphenyl group could come in rather close contact. In the model shown in Figure 1, the aromatic group was oriented so as to mimic the approach of the assumed

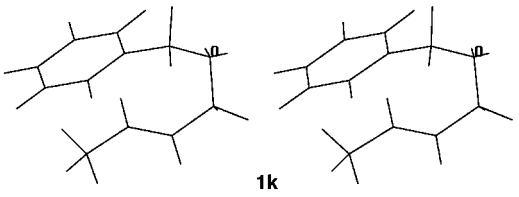
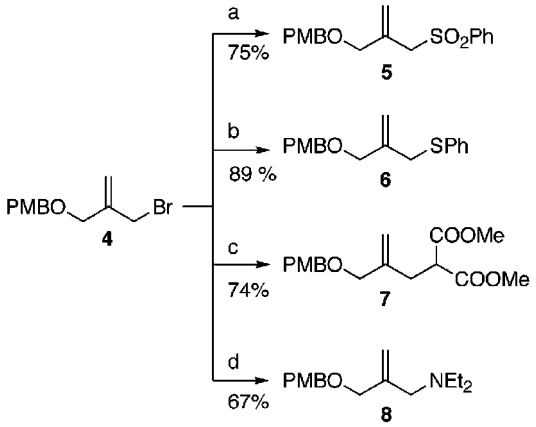


Figure 1. Stereoview of a transition-state model of the rearrangement of **1k**.

Scheme 3[a]

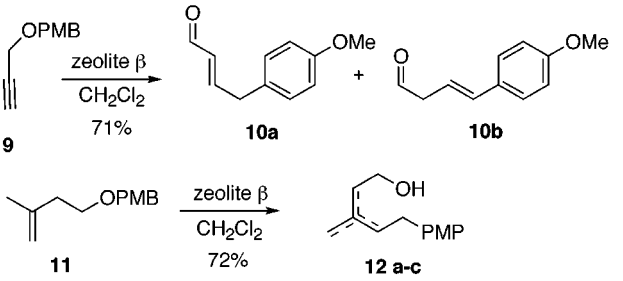


[a] Reaction conditions: (a) $PhSO_2Na$, DMF, rt, 24 h; (b) Cs_2CO_3, PhSH, CH_3CN, rt, 30 min; (c) NaH, dimethylmalonate, THF, rt, 30 min; (d) Et_2NH, CH_3CN, reflux 30 min.

benzylic cation to the terminal olefinic carbon. Since the nascent cation at position 2 would only be secondary, it is possible that the steric repulsion between the aromatic group and the methyl group is sufficient to hinder the reaction. A more favorable tertiary cationic center as in **1f** was, on the other hand, sufficient to allow the reaction despite that there should be a steric hindrance similar to that in **1k**. In the absence of steric crowding as in **1a** and **1i**, the rearrangement proceeded quite well even if the intermediary cation would be secondary. The rapid reaction of **1l** and **1m** may be explained by heterolysis of the other ether bond due to the more favorable formation of prenyl cation. Subsequent reactions of this electrophile with *p*-methoxybenzyl alcohol would then give rise to several products via electrophilic aromatic substitutions.

The results obtained in this work are partly in accordance with the characteristics of the acid-catalyzed rearrangement of allylic alcohols to aldehydes or ketones. In these reactions, protonation of the double bond leads to a carbocation similar to **A** (Scheme 1), which then undergoes a prototropic shift to generate the carbonyl function. It was concluded that allylic systems having the ability to form a tertiary cation reacted smoothly, while those that could only form a secondary cation were unreactive.[7] Thus, this mechanism is closely related to that suggested for the BenzAll rearrangement (Scheme 1),[2] and most of the results presented in this report can be rationalized accordingly. However, **1a** and **1i** did rearrange, although only secondary carbocations may be formed. In contrast, the allylic ethers **4**-**8** (Scheme 3) were not useful in this rearrangement probably because each contains an electronegative substituent on the carbon attached to the carbon that will become positively charged. Thus, the inductive electron-withdrawing effect

Scheme 4



will destabilize the nascent cationic center in particular on Lewis acid coordination of the electronegative substituent.

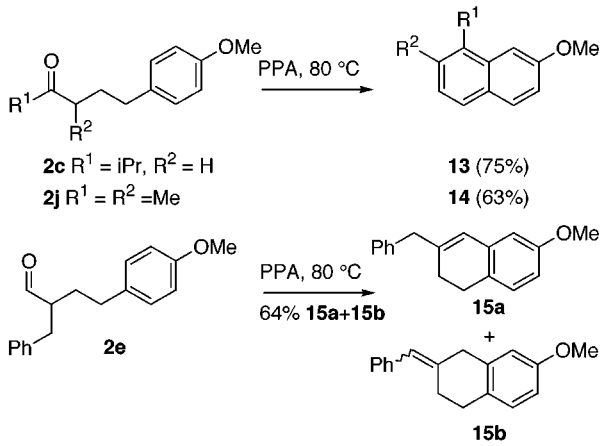
Compound **4**,[8] available in two steps from 3-bromo-2-(bromomethyl)propan-1-ol (DIBOL),[9] was used as starting material for the synthesis of the structurally diverse allylic ethers **5**−**8** via substitution of bromine by different C-, N-, and S-nucleophiles as indicated in Scheme 3.

Also, alkynes should be able to act as π-nucleophiles toward cationic centers. Indeed, propargyl PMB ether **9** on treatment with zeolite β gave **10a** and **10b** (3:1) in 71% total yield (Scheme 4). Double-bond isomerization obviously took place in the presence of the zeolite as judged from GC analyses directly of the reaction mixture. Rearrangement of the homoallylic compound **11** gave a mixture of the three unsaturated alcohols **12a**−**c** in a total yield of 72% (Scheme 4). The carbocation intermediate generated in the first step apparently eliminates a proton from either of three available positions.

The rearrangement products, containing a benzene ring and a four-carbon unit terminated with a carbonyl functionality, are potential precursors for naphthalene derivatives. As zeolites may act as both Brönsted and Lewis acids, we hoped that prolonged reaction times or higher temperatures would result in ring closure in situ. This did not occur with the examples tested here, presumably because the methoxy group was located in the meta position to the carbon that would undergo attack of the electrophile. However, both aldehydes **2c** and **2e** as well as ketone **2j** gave good total yields of naphthalene or hydronaphthalene derivatives on treatment with PPA at 80 °C for 2 h (Scheme 5).[10,11] Obviously, the ring closure was followed by water elimination and oxidation. Since the oxidation occurred in the reaction mixture as indicated by TLC analyses, it was presumably caused by air dissolved in the PPA. In the ring closure of **2e**, a 1:1 mixture of the dihydronaphthalenes **15a** and **15b** was formed, but no oxidation to naphthalenes was noticed.

In conclusion, several allylic PMB ethers rearranged in the presence of zeolite β to form 4-arylbutanals or 5-arylpentan-2-ones depending on the substituent pattern of the allylic part. Best results were obtained with substrates carrying simple substituents in the allylic 2-position. Rearrangement of the 2-chloro-substituted ether **1h** resulted in a moderate yield of the labile α-chloro aldehyde derivative **2h**, which was immediately converted to the phenyl sulfone **3**. However, a number of substrates carrying substituents containing heteroatoms in this position did not give satisfactory results. The products formed in the rearrangement may be cyclized to give dihydronaphthalene and/or naphthalene derivatives. Thus, the entire reaction sequence may be developed into a versatile method for the synthesis of such compounds, some of which are important natural products and drugs.[12−19] These and other aspects of the BenzAll rearrangement are being investigated in our laboratory, and results concerning variation of the aromatic part will be reported in due course.

Scheme 5. Ring Closure to Naphthalene Derivatives



Experimental Section

General Methods. Gas chromatographic analyses were performed on a DB vax (J&W Scientific) capillary column 30 m × 0.25 mm i.d., 0.25 μm stationary phase. NMR spectra were recorded at 300 MHz using $CDCl_3$ as internal standard. Chromatographic separations were performed on Matrex Amicon normal-phase silica gel 60 (0.035−0.070 mm). Thin-layer chromatography was performed on Merck precoated TLC plates with silica gel 60 F-254, 0.25 mm. After eluation, the TLC plates were vizualized with UV light or sprayed with a solution of *p*-methoxybenzaldehyde (26 mL), glacial acetic acid (11 mL), concentrated sulfuric acid (35 mL), and 95% ethanol (960 mL) followed by heating. Mass spectra were recorded in the following modes: EI (70 eV) using both direct inlet and inlet via a gas chromatograph equipped with a DB Wax column as above, CI (CH_4, 200 eV) and FAB. Chemicals were reagent grade. Zeolite β was a gift from EKA Chemicals AB, Bohus, Sweden, and was activated at 400 °C for 3 h before use. Zeolite β is also commercially available.[20] THF was distilled under N_2 from sodium benzophenone ketyl, and CH_2Cl_2 was distilled from P_2O_5 prior to use. DMF and MeCN were stored over 4A molecular sieves. Data for compounds **1b**,**c**,**g**,**j**, **2b**,**c**,**j**,**k**, and **4** can be found elsewhere.[2,8]

Typical Procedure for the Synthesis of Allyl 4-Methoxybenzyl Ethers. 3-[(4-Methoxybenzyl)oxy]-2-phenyl-

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(20) PQ Corporation, Zeolites and Catalysts Division, P.O. Box 840, Valley Forge, PA 19482.

propene (1d). A solution of 2-phenylpropenol (1.34 g, 10 mmol) in THF (5 mL) was slowly added to a suspension of sodium hydride (440 mg,11.0 mmol, 60% in mineral oil) in DMF at 0 °C under Ar followed by stirring for 30 min. 4-Methoxybenzyl chloride (1.61 g, 10.3 mmol) in THF (2 mL) was then added, and the mixture was stirred for 2 h. The mixture was thereafter distributed between ether and water, and the organic phase was washed with water and brine followed by drying ($MgSO_4$). After removal of the solvent under reduced pressure, the residue was purified by chromatography (heptane−EtOAc 95:5), which gave 2.06 g (81%) of **1d**: ^{1}H NMR ($CDCl_3$) δ 7.48 (m, 2 H), 7.30 (m, 5 H), 6.88 (d, 2 H), 5.56 (s, 1 H), 5.37 (s, 1 H), 4.51 (s, 2 H), 4.40 (s, 2 H), 3.81 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 159.2, 144.3, 138.8, 130.3, 129.5, 128.3, 127.8, 126.2, 114.5, 113.8, 71.7, 71.6, 55.3; HRMS calcd for $C_{17}H_{18}O_2$ 254.1307, found 254.1313.

Typical Procedure for the Rearrangement. 4-(4-Methoxyphenyl)-2-phenylbutanal (2d). A solution of **1d** (1.0 mmol) in CH_2Cl_2 (2 mL) was added to activated zeolite β (100 mg) under argon. The reaction mixture was stirred at room temperature, and the progress of the reaction was monitored with TLC. After completion of the reaction (ca. 12 h), the resulting colored mixture was filtered through Celite. The Celite was washed with CH_2Cl_2, and the combined organic extracts were concentrated at reduced pressure. Purification by chromatography (heptane−EtOAc 10:1) gave 147 mg (54%) of **2d**: ^{1}H NMR ($CDCl_3$ δ 9.67 (d, J = 1.8 Hz, 1 H), 7.36 (m, 3 H), 7.20 (m, 2 H), 7.06 (d, J = 8.3 Hz, 2 H), 6.83 (d, J = 8.7 Hz, 2 H), 3.79 (s, 3 H), 3.50 (m, 1 H), 2.55 (m, 2 H), 2.37 (m, 1 H), 2.03 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 200.7, 158.0, 136.1, 133.2, 129.4, 129.1, 129.0, 127.7, 113.9, 58.2, 55.3, 32.0, 31.3; IR (film) 1730 cm^{-1}; HRMS calcd for $C_{17}H_{18}O_2$ 254.1306, found 254.1306.

4-(4-Methoxyphenyl)-2-(phenylsulfonyl)butanal (3). Compound **1h** was treated according to the typical procedure for the rearrangement, but since the product, 2-chloro-4-(4-methoxyphenyl)butanal (**2h**), was unstable, characterization was performed by conversion to the corresponding phenyl sulfone **3**. Thus, crude **2h** was dissolved in DMF (7 mL) followed by addition of the sodium salt of benzene sulfinic acid (330 mg, 2.0 mmol), and the mixture was then stirred for 21 h. Water (10 mL) was added followed by extraction with ether. The combined organic phases were washed with water, dried (Na_2SO_4), and concentrated at reduced pressure. Chromatography (heptane−EtOAc 2:1) gave **3** (168 mg, 53%): ^{1}H NMR ($CDCl_3$) δ 9.72 (d, J = 2.6 Hz, 1 H), 7.79−7.53 (m, 5 H), 7.01 (d, J = 8.6 Hz, 2 H), 6.81 (d, J = 8.7 Hz, 2 H), 3.85 (m, 1 H), 3.79 (s, 3 H), 2.71 (m, 1 H), 2.57 (m, 1 H), 2.26 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 193.2, 158.4, 134.6, 131.1, 129.5, 129.4, 128.9, 128.7, 114.1, 73.7, 55.3, 31.4, 25.4; IR (film) 1730 cm^{-1}; HRMS calcd for $C_{17}H_{18}O_4S$ 318.0925, found 318.0931.

2-[[(4-Methoxybenzyl)oxy]methyl]-3-(phenylsulfonyl)-propene (5). 2-(Bromomethyl)-3-[(4-methoxybenzyl)oxy]propene (**4**)[8] (542 mg, 2.0 mmol) was dissolved in DMF (10 mL), and sodium benzenesulfinate (657 mg, 4.0 mmol) was added. The reaction mixture was stirred for 24 h and then poured into water (10 mL). The aqueous phase was extracted with ether, and the combined ether phases were dried (Na_2SO_4) and concentrated at reduced pressure. Chromatography of the residue (heptane−EtOAc 8:2) gave **5** (532 mg, 75%) as a colorless oil, which crystallized upon standing: mp 51−53 °C; ^{1}H NMR ($CDCl_3$) δ 7.88 (d, J = 7.1 Hz, 2H), 7.59 (m, 3 H), 7.24 (m, 2 H), 6.88 (d, J = 8.7 Hz, 2 H), 5.37 (s, 1 H), 5.01 (s, 1 H), 4.38 (s, 2 H), 3.98 (s, 2 H), 3.86 (s, 2 H), 3.81 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 159.3, 138.4, 134.2, 133.8, 129.9, 129.1, 129.0, 128.5, 121.8, 113.8, 72.1, 71.7, 59.5, 55.3; HRMS (FAB) calcd for $C_{18}H_{20}O_4SNa$ 355.0980, found 355.0959.

3-[(4-Methoxybenzyl)oxy]-2-[(phenylthio)methyl]propene (6). Compound **4**[8] (542 mg, 2.0 mmol) was dissolved in CH_3CN (20 mL), and thiophenol (300 μL, 2.9 mmol) and Cs_2CO_3 (771 mg, 2.37 mmol) were added. The mixture was stirred for 30 min and was then poured into water (100 mL). The water phase was extracted with ether, and the combined ether phases were dried (Na_2SO_4) and concentrated at reduced pressure. Chromatography of the residue (heptane−EtOAc 95:5) gave **6** (535 mg, 89%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.27 (m, 7 H), 6.88 (d, J = 8.7 Hz, 2 H), 5.11 (s, 1 H), 5.02 (s, 1 H), 4.42 (s, 2 H), 4.09 (s, 2 H), 3.79 (s, 3 H), 3.61 (s, 2 H); ^{13}C NMR ($CDCl_3$) δ 159.2, 141.5, 130.1, 129.0, 128.9, 128.8, 126.3, 125.9, 115.6, 113.8, 71.9, 71.2, 55.3, 37.4; HRMS calcd for $C_{18}H_{20}O_2S$ 300.1184, found 300.1183.

Dimethyl [2-[[(4-methoxybenzyl)oxy]methyl]allyl]malonate (7). Dimethyl malonate (528 mg, 4.0 mmol) in THF (20 mL) was added to a slurry of NaH (100 mg, 2.5 mmol, 60% in mineral oil) in THF (5 mL). The mixture was stirred for 15 min, whereafter **4**[8] (542 mg, 2.0 mmol) in THF (10 mL) was added dropwise. Stirring was continued for 3 h, and then THF was evaporated at reduced pressure. The residue was distributed between ether and water, the combined ether phases were dried, and the solvent was removed under reduced pressure. Chromatography of the residue (heptane−EtOAc 8:2) gave **8** (477 mg, 74%) as a colorless liquid: ^{1}H NMR ($CDCl_3$) δ 7.28 (d, J = 8.6 Hz, 2 H), 6.87 (d, J = 8.7 Hz, 2 H), 5.11 (s, 1 H), 4.98 (s, 1 H), 4.41 (s, 2 H), 3.94 (s, 2 H), 3.80 (s, 3 H), 3.72 (s, 6 H), 3.68 (t, J = 7.8 Hz, 1 H), 2.67 (d, J = 7.8 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 169.4, 159.2, 142.3, 130.9, 129.4, 114.3, 113.8, 72.5, 71.6. 55.3, 52.6, 50.3, 41.1; IR (film) 1730 cm^{-1}; HRMS (FAB) calcd for $C_{17}H_{22}O_6Na$ 345.1314, found 345.1321.

3-[(4-Methoxybenzyl)oxy]-2-[(dimethylamino)methyl]-propene (8). A solution of diethylamine (293 mg, 4.0 mmmol) in CH_3CN (25 mL) was added to **4**[8] (542 mg, 2.0 mmol). The mixture was refluxed for 30 min, whereafter water (25 mL) was added and the CH_3CN was evaporated at reduced presssure. The aqueous phase was extracted with CH_2Cl_2, and the combined organic phase was dried (Na_2SO_4) and concentrated at reduced pressure. Chromatography of the residue (heptane−EtOAc 8:2 + 1% triethylamine) gave **7** (352 mg, 67%) as a yellow liquid: ^{1}H NMR ($CDCl_3$) δ 7.29 (d, J = 8.7 Hz, 2 H), 6.88 (d, J = 8.7 Hz, 2 H), 5.18 (s, 1H), 5.11 (s, 1 H), 4.43 (s, 2 H), 4.01 (s, 2 H), 3.80 (s, 3 H), 3.03 (s, 2 H), 2.47 (q, J = 7.1 Hz, 4 H), 1.01 (t, J = 7.1 Hz, 6 H); ^{13}C NMR ($CDCl_3$) δ 159.1, 144.6, 142.7, 129.2, 113.7, 113.4, 71.9, 71.5, 56.6, 55.3, 46.7, 11.7; HRMS calcd for $C_{16}H_{26}NO_2$ (M + H) 264.1964, found 264.1960.

Cyclization with PPA. Synthesis of 2-Methoxy-7-(methylethyl)naphthalene (13). A mixture of aldehyde **2c** (220 mg, 1.0 mmol) and PPA (1 mL) was stirred at 80 °C for 2 h and then cooled to room temperature. Aqueous 10% NaOH (10 mL) was then added followed by extraction with ether. The combined organic phases were washed with water and saturated aqueous $NaHCO_3$ and then again with water. After drying of the organic extract ($MgSO_4$), the solvent was removed under reduced pressure. Chromatography (heptane−EtOAc 8:2) of the residue gave **13** (151 mg, 75%): ^{1}H NMR ($CDCl_3$) δ 7.69 (m, 2 H), 7.57 (m, 1 H), 7.27 (m, 1 H), 7.08 (m, 2 H), 3.93 (s, 3 H), 3.04 (m, 1 H), 1.34 (d, J = 6.9 Hz, 6 H); ^{13}C NMR ($CDCl_3$) δ 157.0, 146.7, 142.7, 134.8, 129.0, 127.6, 123.5, 123.1, 117.8, 105.6, 55.3, 34.3, 24.0; HRMS calcd for $C_{14}H_{16}O$ 200.1201, found 200.1202.

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Supporting Information Available: ^{13}C NMR spectra for all compounds analyzed by HRMS. Data for compounds **1a**,**e**,**f**,**h**,**i**,**k**−**n**, **2a**,**e**,**f**,**i**, **9**, **10a**,**b**, **11**, **12a**−**c**, **14**, and **15a**,**b** (27 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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