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Trimethoxyarene as a Highly Ionizable Tag for Reaction Analysis by Atmospheric Pressure Photoionization Mass Spectrometry (APPI/MS): Exploration of Heterocyclic Synthesis

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A mass spectrometry (MS) method was developed to rapidly analyze crude reaction mixtures. This method relies on highly effective ionization by atmospheric pressure photoionization (APPI) of molecules with a prosthetic trimethoxyarene (TMOA) residue. In a crude reaction mixture, products resulting from the reaction of the TMOA-labeled substrate will be selectively ionized to afford an easily readable mass spectrum. Interestingly, we noticed that TMOA-labeled molecules were not fragmented and gave the preferred $[M + H]^+$ ion peak. This APPI-MS reaction mixture analysis method was used for the optimization of heterocycle synthesis. By comparing results obtained by APPI/MS, GC, and HPLC analysis, it appeared that a semi-quantification could be achieved by integrating the MS peak intensities.

Introduction

High-throughput analytical methods[1] based on IR thermography,[2] fluorescence,[3] colorimetric assays,[4] immunoassay,[5] mass spectrometry (MS) analysis,[6] have been developed to monitor chemical reactions and catalysts. These methods are very powerful and are well suited for the screening of large numbers of similar reactions; however, they are less proficient for evaluating multistep organic reactions. For instance, they often cannot distinguish between products, byproducts, and molecules resulting from decomposition of the starting chemicals. Consequently, these methods appear to be tailored to optimize high-value industrial reactions, but are less flexible to deal with a wide variety of chemical reactions.

To address this particular problem, more suitable and versatile methods have been developed by using equipment available in chemical laboratories. For example, serial and fast analytical methods (such as TLC, GC, and HPLC) can identify products and/or quantify yields.[7] These methods aim to facilitate the routine work of organic chemists by rapidly evaluating the composition of crude reaction mixture, a vital information for reaction optimization.

One valuable technique that has been developed is atmospheric pressure photoionization (APPI) coupled to MS, which enables the analysis of mixtures of nonpolar and low-molecular-mass compounds; a feature frequently found in organic synthesis.[8] Previously, the groups of Chen[8d,8g] and Wilson[8h,8i] demonstrated that labeling a catalyst or biomolecule with an ionizable prosthetic cation or with an ionophore was a valuable tool for detecting the catalyst or biomolecule by using a combination of electrospray ionization and MS (ESI-MS). Herein, we report on the use and validation of APPI-MS as a tool to rapidly monitor organic reactions by using tagged substrates. We have used trimethoxybenzene as a tag that significantly enhanced the MS sensitivity and enabled us to obtain an overview of the various adducts formed at the expense of the labeled substrates.

Results and Discussion

APPI is used as a soft ionization technique that, under given conditions, preferentially generates $[M + H]^+$ ions by proton transfer and minimizes fragmentation.[8] Unfortunately, when using this method to quantitatively analyze crude reaction mixtures, the chemical properties of the analytes and the presence of reagents or catalysts can affect the analysis of the different products.

To overcome these limitations, we decided to label one of the reaction partners with a molecular tag compatible with the APPI ionization source. After testing a large variety of molecules, including polyaromatics, natural products,

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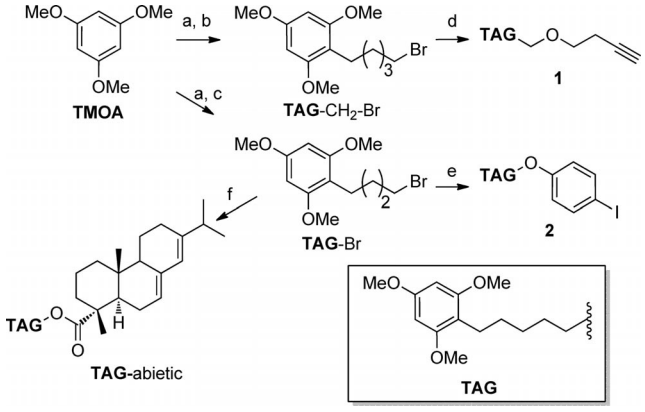
heterocycles, and synthetic intermediates, we found that the 1,3,5-trimethoxyarene (TMOA) fragment was highly sensitive to APPI ionization and provided intense ions due to its high proton affinity, relative to the other compounds tested.[9] To facilitate the introduction of the TMOA label, alkyl spacers were attached to the substrates under study. TMOA handles (TAG-Br, TAG-CH_2Br) were obtained by BuLi deprotonation of 1,3,5-trimethoxybenzene followed by reaction with an excess of 1,5-dibromopentane or 1,6-dibromohexane (Scheme 1). This approach is rapid and easy to implement because the crude mixture is injected into the MS device without any prior treatment.



Scheme 1. Reagents and conditions: (a) *n*BuLi, 0 °C, THF, 1 h; (b) 1,6-dibromohexane; (c) 1,5-dibromopentane; (d) NaH, DMF, –10 °C, then 4-bromobutynol, –10 °C, 1 h; (e) NaH, DMF, 0 °C, then 4-iodophenol, 80 °C, 16 h; (f) abietic acid, Cs_2CO_3, DMF.

To validate this approach, native abietic acid and TAG-abietic were submitted to APPI-MS analyses (Figure 1).

Abietic acid was selected as a nonpolar and low-molecular-weight compound (MW = 538 Da) to represent routine adducts encountered in organic synthesis. Thus, both native abietic acid and TAG-abietic ester were analyzed by APPI-MS under our optimized conditions. Interestingly, the TMOA-labeled molecule was detected as a single intense $[M + H]^+$ ion at *m/z* 539, whereas the native compound yielded a complex picture of peaks from which the molecular ion was absent.[9] Interestingly, Wilson and Wu reported comparable observations with vitamin D_3 labeled with a crown ether when using ESI-MS detection in diluted conditions.[8i]

Next, TMOA tags were evaluated in a commonly used chemical transformation: the Sonogashira coupling. The performance of the APPI-MS method was compared with other analytical methods (HLPC or GC). The tagged alkyne substrate **1** (MW = 320 Da) was prepared by treating TAG-CH_2Br with 4-bromobutynol. The Sonogashira reaction was then performed with iodobenzene in presence of several additives in THF at 50 °C (Table 1).

To determine the conversion of the reaction with the APPI-MS method, aliquots of the crude reaction mixture were infused directly in the MS without prior purification. It was anticipated that only the tagged compounds (**1**, **3**, and side products, if any were present) would respond

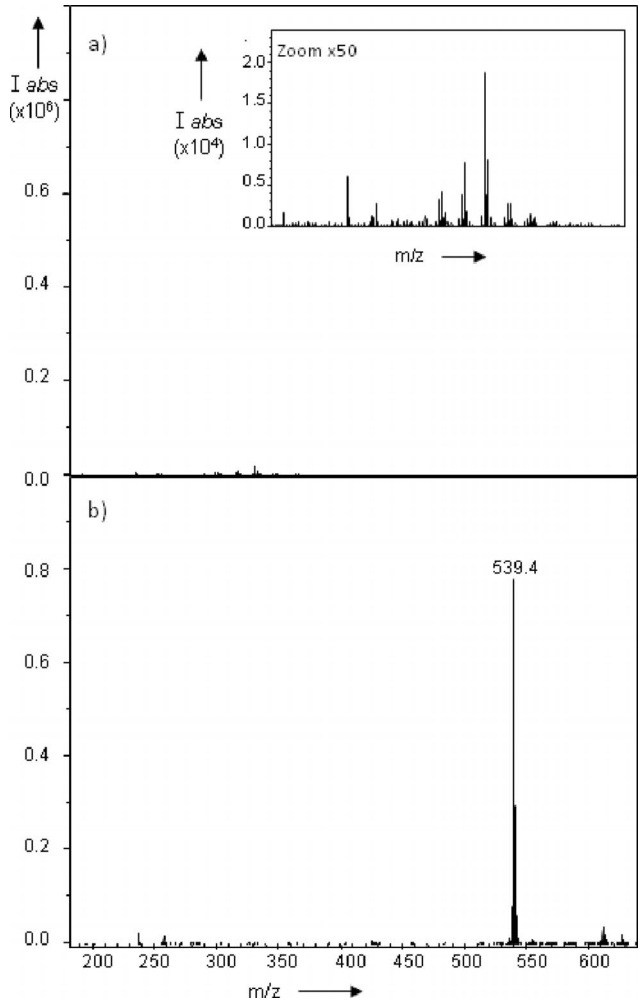


Figure 1. APPI-MS analysis of (a) abietic acid and (b) TAG-abietic. Spectra were recorded by flow injection analysis (1 μL sample at 5×10^{-4} M sample injection) of samples in a mixture of MeOH/toluene (8:2). Both mass spectra are on the same absolute intensity scale.

Table 1. Comparison of the yields of the Sonogashira reaction by APPI-MS, HPLC and GC.

Entry[a]	Additive	Yield [%][b]		
		GC	HPLC	APPI-MS[c]
1	CuBr	44	43	42
2	CuCl	43	43	43
3	CuI	40	44	45
4	Cu_2O	60	55	61
5	Ag_2CO_3	8	11	12

[a] Conditions: **1** (1 equiv.), iodobenzene (1.2 equiv.), [$Pd(PPh_3)_2Cl_2$] (0.04 equiv.), additive (0.1 equiv.), THF/aqueous NH_3, 50 °C, 12 h. [b] The yields were determined by the ratio of the area of the selected peak to the total area of all peaks. [c] Representative procedure for APPI/MS analyses: a sample of the crude mixture (9 μL) was added to a mixture of MeOH/toluene (991 μL 8:2) to give a final concentration of 5×10^{-4} M (based on starting material), then an aliquot (5 μL) was injected into the mass spectrometer.

strongly to the APPI analysis. In these experiments the yields were not optimized and the reactions were stopped before completion. Indeed the mass spectrum displayed only two peaks at *m*/*z* 321 and 397, which corresponded to starting protonated alkyne **1** and to the protonated Sonogashira adduct **3** (*MW* = 396 Da), respectively. Interestingly, a peak at *m*/*z* 640 could be detected in all crude reaction mixtures and corresponded to a small amount of the diyne formed by the homocoupling of **1**. The peak ratio **1/3** is directly correlated to the chemical conversion of **1** and to the yield of **3**. These results agreed with HPLC and GC analyses of the respective reaction aliquots (Table 1). As expected, Cu^I was an excellent additive with respect to Ag^I (44–60% yield with Cu^I, 8% with Ag^I). Thus, excellent correlations were found among the three methods, even for the low conversion with Ag^I. To evaluate the application of the APPI/MS-TMOA analytic method for the optimization of elaborated chemical reactions, we decided to focus on the syntheses of N-heterocycles. To extend the scope of Mori's one-pot, four-component pyrazole synthesis[10] to other class of heterocycles, we substituted the hydrazine with other nitrogen dinucleophiles, such as phenylamidine (**5**), aminopyrazole (**6**), aminobenzimidazole (**7**) (Figure 2).

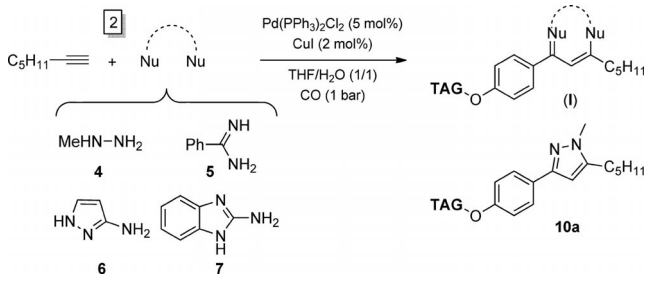


Figure 2. Mori's multicomponent reaction with a series of dinucleophiles.[10]

In this one-pot reaction, the formation of ynone **9a** by alkynylcarbonylation, assisted by Pd^0, was expected to proceed in situ and to directly react with the dinucleophilic reagent through Michael addition. Further dehydration should deliver the expected heterocycles of type **I**. Thus, compounds **2**, **3**, and **4** were treated with $[PdCl_2(PPh_3)_2]$ and CuI in a mixture of THF/H_2O (1:1) under a blanket of CO. By using a modification of Mori's procedure,[9] pyrazole **10a** (Figure 2) was identified by APPI-MS in the crude reaction mixture in 95% yield. Purification by column chromatography afforded the product in 79% yield and NMR spectroscopic analysis confirmed the structure of pyrazole **10a** contaminated with a regioisomer (less than 5%).

Next, the one-pot, four-component reaction was attempted with dinucleophiles **5**, **6**, and **7**. However, unknown products were observed, for instance, MS analysis of the crude mixture for the reaction with **5** did not lead to the expected pyrimidine adduct **11a** (Figure 4), but produced a $[M + H]^+$ ion at *m*/*z* 477, corresponding to a molecular mass at 476 Da. The latter was attributed to acylbenzamidine **8**, which was obtained as a consequence of the direct addition of **5** to the acylpalladium intermediate derived from **2**. The structure of **8** was unambiguously confirmed by synthesis followed by NMR spectroscopic analysis.[9,11] Interestingly, the ability to detect unexpected side products by APPI-MS/TMAO analysis may provide a hint to understand the failure of the one-pot, four-component reaction (Figure 3).

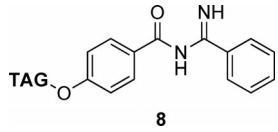


Figure 3. Structure of **8**, a side product obtained in the four-component sequence with **5** as the nucleophile.

Therefore, we decided to use a sequential two-step procedure for dinucleophiles **5**–**7**. First, ynone **9a** was prepared by a carbonylative Sonogashira reaction (**2**, alkyne, CO) and submitted reaction with dinucleophiles **4**–**7** for the heterocyclization step under various reaction conditions (Figure 4). The reaction mixtures were first analyzed by APPI-MS using our optimized protocol and the tagged heterocyclic adducts **10a**–**13a** were identified by their corresponding $[M + H]^+$ ions. The yields were evaluated by the ratio of the intensity of the expected isotopic mass of the compound with the sum of the intensity of all detected peaks. The results are depicted in Figure 4 by using a color code to indicate the percentage yield of each reaction. As expected, reactions with nucleophile **4** proceeded successfully in all conditions. Reactions with **5** and **6** gave satisfactory yields with K_2CO_3 in neat conditions or in a mixture of THF/H_2O. The condensation of **9a** with **7** showed a strong solvent dependency: the cyclodehydration went to completion in THF/H_2O, but did not proceed in CH_2Cl_2.

To confirm the accuracy of the APPI-MS/TMOA method, the crude reaction mixtures were also analyzed by ^1H NMR spectroscopy (Figure 4, right box). A comparison of the estimated yields obtained by APPI-MS and ^1H NMR spectroscopy revealed good overall consistency. Nucleophile **6** was the exception (Figure 4): the yield of the formation of pyrazolo-pyrimidine **12a** was slightly overestimated by APPI-MS (APPI-MS indicated 38% yield of **12a**, whereas a yield of 15% was determined by ^1H NMR spectroscopy). Indeed, the presence of a basic site seems to enhance the proton affinity of the substrate, and therefore, yields a higher peak in APPI-MS. Nevertheless, the results obtained demonstrate that the APPI-MS/TMOA method is a reliable and rapid tool for determining optimal productive reaction conditions.

Finally, for each dinucleophile of **4**–**7**, the most efficient reaction conditions were selected and applied to the unlabeled ynone **9b** (R = Me instead of R = TAG). Adducts **10b**, **11b**, **12b**, and **13b** were isolated by column chromatography and analyzed by ^1H NMR spectroscopy. As expected, high yields were obtained in all cases. It is noteworthy that **10b** and **12b** were contaminated by regioisomers **10b′** (**10b**/**10b′**: 95:5) and **12b′** (**12b**/**12b′**: 90:10) and they could be sepa-

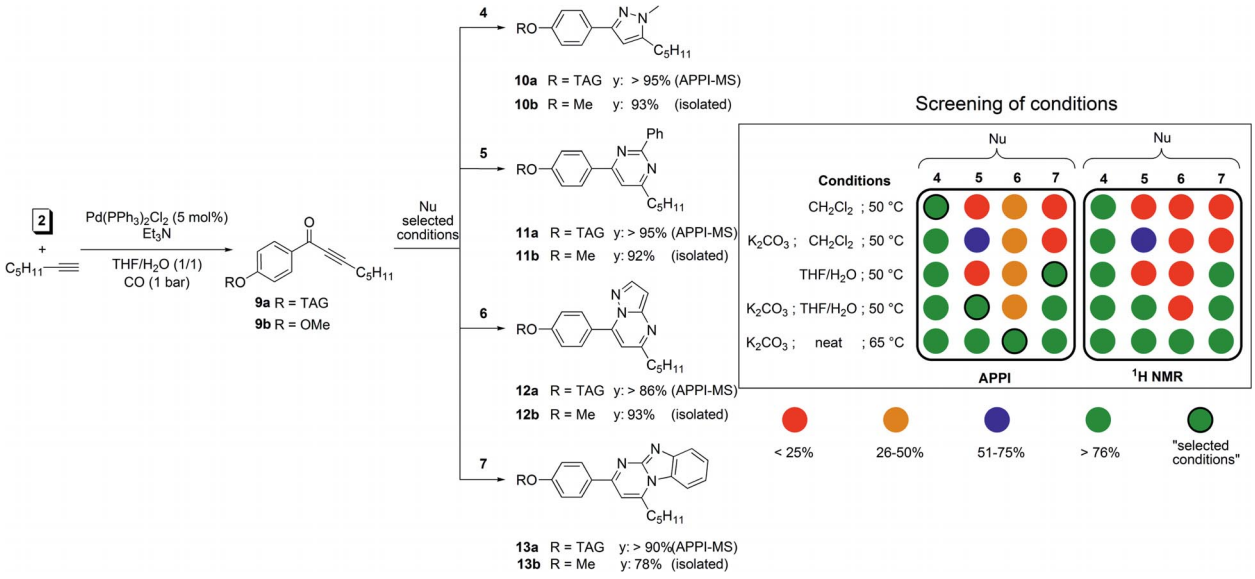


Figure 4. Screening of cyclodehydration reaction conditions. Synthesis of heterocycles **10b**, **11b**, **12b**, and **13b**. Conditions: the reagents are indicated above the arrows; the duration of the carbonylation is 24 h at room temp. and 48 h at 50 °C for the heterocyclization. For easy readability, yields are indicated by using a color code: red for yields < 25%, orange for yields between 25 and 50%, blue for yields between 51% and 75%, and green for yields above 76%.

rated by chromatography. In contrast, the reaction of **9b** with **7** afforded **13b** as a single regioisomer. Ynones have been largely used with methylhydrazine and benzamidine for the construction of combinatorial libraries of pyrazoles[12] and pyrimidines,[13] whereas the reactions between ynone and 2-aminobenzimidazole or 3-aminopyrazole have scarcely been described.[14] The APPI-MS/TMOA method has enabled us to successfully and rapidly optimize the reaction conditions of these reactions.

Conclusions

The TMOA fragment was identified as a label with a high ionization potential. Therefore, when a substrate was tagged with TMOA, chemical transformations could be followed conveniently by MS/APPI and applications towards the syntheses of heterocycles were developed. Other benefits of the procedure are (i) the direct overview of the composition and conversion (semiquantitative yield) of crude reaction mixtures and (ii) the detection of side products. Further studies are currently ongoing towards the development of a second-generation tag with an improved selectivity of ionization for the APPI-MS mode.

Experimental Section

General: All reagents were used as purchased from commercial suppliers without further purification. Solvents were dried and purified by conventional methods prior to use. THF was freshly distilled from sodium/benzophenone and dichloromethane was distilled from CaH_2. Flash column chromatography was performed with Merck silica gel 60, 0.040–0.063 mm (230–400 mesh). Merck aluminum-backed plates precoated with silica gel 60 (UV_{254}) were used for TLC and were visualized by staining with $KMnO_4$. ^1H and ^{13}C NMR spectra were recorded on Bruker spectrometers (400 and 100, 300 and 75, and 200 and 50 MHz, respectively). Conditions are specified for each spectrum (temperature 25 °C unless specified). Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; quint, quintet; m, multiplet. Chemical shifts (δ) are given in ppm relative to the resonance of their respective residual solvent peak, $CHCl_3$ (δ = 7.27 ppm, ^1H; 77.16 ppm, the middle peak, ^{13}C). IR spectra were recorded with a Nicolet 380 FTIR spectrometer. High-resolution mass spectroscopy analyses were conducted by the Institut Fédératif de Recherche 85 at the University of Strasbourg, and low-resolution APPI mass spectrometry analyses were conducted by Novalix. APPI-MS experiments were carried out by using a MSD mass spectrometer equipped with an APPI source (Agilent Technologies) and a quadrupole mass analyzer. High-resolution mass spectra were obtained with a Bruker Micro-TOF-Q (ESI q-TOF, positive ion) spectrometer. Melting points were determined on a Büchi Melting Point B-540 apparatus in open capillary tubes.

2-(6-Bromohexyl)-1,3,5-trimethoxybenzene (TAG-CH_2Br): 1.6 M *n*BuLi (8.9 mL, 14.2 mmol, 1.2 equiv.) was added to a solution of 1,3,5-trimethoxybenzene (2.00 g, 11.9 mmol, 1 equiv.) in THF (60 mL) at 0 °C under an argon atmosphere. The reaction mixture was stirred for 30 min at 0 °C then for 1 h at room temperature. 1,6-Dibromohexane (5.4 mL, 35.7 mmol, 3 equiv.) was added at 0 °C and the reaction mixture was stirred at 0 °C for 30 min and for 1 h at room temperature. Water (15 mL) and ethyl acetate (15 mL) were added and the aqueous layer was extracted with ethyl acetate (3 × 15 mL). The combined organic layers were dried with Na_2SO_4, filtered, and evaporated under reduced pressure. Excess 1,6-dibromohexane was removed by distillation. The residue was purified by column chromatography on silica gel (pentane/ethyl acetate, 97:3) to give TAG-CH_2Br as a colorless solid (3.4 g, 86%); m.p. 58–59 °C. ^1H NMR ($CDCl_3$, 300 MHz): δ = 6.20 (s, 2 H), 3.83 (s, 3 H), 3.80 (s, 6 H), 3.48 (t, J = 6.7 Hz, 2 H), 2.57 (t, J = 6.9 Hz, 2 H), 1.89–1.46 (m, 6 H) ppm. IR (neat): $\tilde{\nu}$ = 2955, 2928, 2854, 2836, 1590 cm^{-1}. HRMS (ESI): calcd. for $C_{15}H_{23}BrO_3$ $[M + H]^+$ 331.0908; found 331.0912.

2-(5-Bromopentyl)-1,3,5-trimethoxybenzene (TAG-Br): 1.6 M *n*BuLi (8.9 mL, 14.2 mmol, 1.2 equiv.) was added to a solution of 1,3,5-trimethoxybenzene (2.00 g, 11.9 mmol, 1 equiv.) in THF (60 mL) at 0 °C under an argon atmosphere. The reaction mixture was stirred for 30 min at 0 °C then for 1 h at room temperature. 1,5-Dibromopentane (4.8 mL, 35.7 mmol, 3 equiv.) was added at 0 °C and the reaction mixture was stirred at 0 °C for 30 min and for 1 h at room temperature. Water (15 mL) and ethyl acetate (15 mL) were added and the aqueous layer was extracted with ethyl acetate (3 × 15 mL). The combined organic layers were dried with Na_2SO_4, filtered, and evaporated under reduced pressure. Excess 1,5-dibromopentane was removed by distillation. The residue was purified by column chromatography on silica gel (pentane/ethyl acetate, 97:3) to give TAG-Br as a colorless solid (2.79 g, 74%); m.p. 49–50 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 6.14 (s, 2 H), 3.81 (s, 3 H), 3.80 (s, 6 H), 3.42 (t, ^3J = 6.8 Hz, 2 H), 2.57 (t, ^3J = 6.8 Hz, 2 H), 1.91 (quint, ^3J = 6.8 Hz, 2 H), 1.48–1.46 (m, 4 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 159.2, 158.8, 111.5, 90.6, 55.7, 55.4, 34.2, 32.8, 28.6, 28.2, 22.2 ppm. IR (neat): $\tilde{\nu}$ = 2955, 2928, 2854, 2836, 1590 cm^{-1}. HRMS (ESI): calcd. for $C_{14}H_{21}BrO_3$ [M + H]$^+$ 317.0747, 319.0728; found 319.0734.

5-(2,4,6-Trimethoxyphenyl)pentyl Abieta-7,13-dien-18-oate (TAG-abietic): Cs_2CO_3 (487 mg, 1.5 mmol, 1.5 equiv.) was added to a solution of abietic acid (453 mg, 1.5 mmol, 1.5 equiv.) in DMF (5 mL) at 0 °C under argon atmosphere. The mixture was stirred for 5 min at room temperature and then TAG-Br (316 mg, 1 mmol, 1 equiv.) was added at 0 °C. The mixture was stirred during 6 h at 0 °C and 1.5 h at 80 °C. The reaction was quenched by the addition of water and the mixture was extracted with ethyl acetate. The combined organic layers were washed with brine, dried with Na_2SO_4, filtered, and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (cyclohexane/ethyl acetate, 95:5) to give TAG-abietic as a waxy oil (219 mg, 40%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 6.13 (s, 2 H), 5.77 (s, 1 H), 5.37 (m, 1 H), 4.02 (m, 2 H), 3.81 (s, 3 H), 3.79 (s, 6 H), 2.55 (t, ^3J = 7.6 Hz, 2 H), 2.30–1.10 (m, other aliphatic protons), 1.27 (s, 3 H), 1.02 (d, ^3J = 6.8 Hz, 3 H), 1.00 (d, ^3J = 6.8 Hz, 3 H), 0.83 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 178.6, 159.2, 158.9, 145.2, 135.5, 122.6, 120.9, 111.7, 90.6, 64.8, 55.7, 55.4, 51.0, 46.6, 45.2, 38.4, 37.2, 35.0, 34.6, 29.1, 28.5, 27.5, 25.8, 25.7, 22.6, 22.3, 21.5, 20.9, 18.3, 17.1, 14.1 ppm. IR (neat): $\tilde{\nu}$ = 2931, 2835, 1717, 1593 cm^{-1}. HRMS (ESI): calcd. for $C_{34}H_{50}O_5$ for [M + H]$^+$ 539.3731; found 539.3726.

2-[6-(But-3-ynyloxy)hexyl]-1,3,5-trimethoxybenzene (1): NaH (60 wt.-%, 1.45 g, 36.2 mmol, 1.2 equiv.) was added to a solution of 3-butyn-1-ol (2.51 mL, 33.2 mmol, 1.1 equiv.) in DMF (200 mL) at –10 °C under argon atmosphere. The reaction mixture was stirred for 1 h at –10 °C and then TAG-CH_2-Br (10.0 g, 30.1 mmol, 1 equiv.) was added. The reaction mixture was stirred at –10 °C for 1 h. Water (200 mL) and ethyl acetate (200 mL) were added and the aqueous layer was extracted with ethyl acetate (3 × 200 mL). The combined organic layers were dried with $MgSO_4$, filtered, and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (cyclohexane/ethyl acetate, 98:2) to give **1** as a white solid (4.2 g, 44%); m.p. 51–52 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 6.13 (s, 2 H), 3.81 (s, 3 H), 3, 79 (s, 6 H), 3.55 (t, ^3J = 7.0 Hz, 2 H), 3.45 (t, ^3J = 6.6 Hz, 2 H), 2.54 (t, ^3J = 7.6 Hz, 2 H), 2.47 (dt, ^3J = 7.2, ^4J = 2.6 Hz, 2 H), 1.98 (t, ^4J = 2.6 Hz, 1 H), 1.62–1.55 (m, 2 H), 1.47–1.39 (m, 2 H), 1.36–1.34 (m, 4 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 159.1, 158.9, 112.1, 90.7, 81.6, 71.4, 69.3, 68.8, 55.8, 55.4, 29.7, 29.6, 26.0, 22.5, 20.0 ppm. HRMS (ESI): calcd. for $C_{19}H_{29}O_4$ [M + H]$^+$ 321.2060; found 321.2072.

2-[5-(4-Iodophenoxy)pentyl]-1,3,5-trimethoxybenzene (2): NaH (60%) (607 mg, 15.1 mmol, 1.2 equiv.) was added to a solution of 4-iodophenol (3.34 g, 15.1 mmol, 1.2 equiv.) in DMF (45 mL) at 0 °C under an argon atmosphere. The reaction mixture was stirred for 10 min at room temperature and then TAG-Br (4.0 g, 12.6 mmol, 1 equiv.) was added. The reaction mixture was stirred at 80 °C overnight. Water (25 mL) and ethyl acetate (25 mL) were added and the aqueous layer was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were dried with Na_2SO_4, filtered, and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (pentane/ethyl acetate, 8:2) to give **2** as white crystals (4.61 g, 80%); m.p. 86–87 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.54 (d, ^3J = 8.7 Hz, 2 H), 6.67 (d, ^3J = 8.7 Hz, 2 H), 6.13 (s, 2 H), 3.91 (t, ^3J = 6.8 Hz, 2 H), 3.81 (s, 3 H), 3.79 (s, 6 H), 2.58 (t, ^3J = 7.0 Hz, 2 H), 1.80 (quint, ^3J = 6.8 Hz, 2 H), 1.50–1.46 (m, 4 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 159.2, 158.9, 138.2, 117.0, 111.6, 90.6, 82.4, 68.3, 55.7, 55.4, 29.2, 29.1, 25.9, 22.4 ppm. IR (neat): $\tilde{\nu}$ = 2935, 2836, 1588 cm^{-1}. HRMS (ESI): calcd. for $C_{20}H_{26}IO_4$ [M + H]$^+$ 457.0870; found 457.0879.

1,3,5-Trimethoxy-2-{6-[(4-phenylbut-3-ynyl)oxy]hexyl}benzene (3): Compound **3** was obtained as an orange oil by following the conditions described in Table 1. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.40 (m, 2 H), 7.28 (m, 3 H), 6.13 (s, 2 H), 3.81 (s, 3 H), 3,79 (s, 6 H), 3.63 (t, ^3J = 7.2 Hz, 2 H), 3.49 (t, ^3J = 6.7 Hz, 2 H), 2.69 (t, ^3J = 7.2 Hz, 2 H), 2.55 (t, ^3J = 7.3 Hz, 2 H), 1.63–1.53 (m, 2 H), 1.36–1.44 (m, 6 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 159.1, 158.9, 131.7, 128.3, 127.8, 123.8, 112.1, 90.6, 87.0, 81.5, 71.4, 69.1, 55.7, 55.4, 29.8, 29.6, 26.1, 22.5, 20.9 ppm. HRMS (ESI): calcd. for $C_{25}H_{33}O_4$ [M + H]$^+$ 397.2373; found 397.2374.

***N*-[Imino(phenyl)methyl]-4-{[5-(2,4,6-trimethoxyphenyl)pentyl]-oxy}benzamide (8):** [$PdCl_2(PPh_3)_2$] (7.5 mg, 0.01 mmol, 0.05 equiv.), H_2O (1.5 mL), K_2CO_3 (91 mg, 0.6 mmol, 3 equiv.), and **5** (68 mg, 0.4 mmol, 2 equiv.) were added successively to a solution of **2** (100 mg, 0.2 mmol, 1 equiv.) in THF (1.5 mL). Carbon monoxide was bubbled through the solution and the reaction was stirred for 36 h under an atmosphere of carbon monoxide (balloon filled with carbon monoxide) at room temperature. Water was added and then the mixture was extracted with ethyl acetate, the combined organic layers were dried with Na_2SO_4, filtered, and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (cyclohexane/ethyl acetate, 7:3) to give **8** as white solid (59 mg, 56%); m.p. 117–119 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.34 (d, ^3J = 8.8 Hz, 2 H), 8.03 (d, ^3J = 8.8 Hz, 2 H), 7.58 (d, ^3J = 8.8 Hz, 2 H), 7.50 (d, ^3J = 7.6 Hz, 2 H), 6.94 (d, ^3J = 8.8 Hz, 2 H), 6.14 (s, 2 H), 4.04 (t, ^3J = 6.5 Hz, 2 H), 3.81 (s, 3 H), 3.79 (s, 6 H), 2.61 (t, ^3J = 6.8 Hz, 2 H), 1.85 (quint, ^3J = 6.5 Hz, 2 H), 1.53–1.51 (m, 4 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 180.1, 166.2, 162.7, 159.1, 158.8, 135.4, 132.3, 131.8, 130.2, 128.9, 127.5, 113.9, 111.7, 90.6, 68.3, 55.7, 55.4, 29.2, 29.1, 26.0, 22.4 ppm. IR (neat): $\tilde{\nu}$ = 3338, 2930, 2849, 2358, 1592, 1543 cm^{-1}. HRMS (ESI): calcd. for $C_{28}H_{32}N_2O_5$ [M + H]$^+$ 477.2384; found 477.2386.

1-(4-{[5-(2,4,6-Trimethoxyphenyl)pentyl]oxy}phenyl)oct-2-yn-1-one (9a): [$PdCl_2(PPh_3)_2$] (138 mg, 0.19 mmol, 0.03 equiv.), H_2O (20 mL), Et_3N (2.7 mL, 19.5 mmol, 3 equiv.), and 1-heptyne (1.7 mL, 13.1 mmol, 2 equiv.) were added successively to a solution of **2** (3.0 g, 6.5 mmol, 1 equiv.) in CH_2Cl_2 (20 mL). Carbon monoxide was bubbled through the solution and the reaction was stirred for 24 h under an atmosphere of carbon monoxide (balloon filled with carbon monoxide) at room temperature. Water was added and then the mixture was extracted with ethyl acetate, the

combined organic layers were dried with Na_2SO_4, filtered, and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (cyclohexane/ethyl acetate, 9:1) to give **9a** as a red oil (2.8 g, 94%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.10 (d, ^3J = 8.7 Hz, 2 H), 6.93 (d, ^3J = 8.7 Hz, 2 H), 6.13 (s, 2 H), 4.03 (t, ^3J = 6.5 Hz, 2 H), 3.80 (s, 3 H), 3.79 (s, 6 H), 2.60 (t, ^3J = 6.8 Hz, 2 H), 2.48 (t, ^3J = 7.1 Hz, 2 H), 1.85 (quint, ^3J = 6.5 Hz, 2 H), 1.68 (quint, ^3J = 7.1 Hz, 2 H), 1.52–1.27 (m, 8 H), 0.94 (t, ^3J = 7.0 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 176.8, 163.9, 159.0, 158.6, 131.7, 129.9, 114.0, 111.2, 95.7, 90.3, 79.6, 68.3, 55.4, 55.1, 31.0, 29.0, 28.8, 27.5, 25.7, 22.2, 22.0, 19.0, 13.8 ppm. IR (neat): $\tilde{\nu}$ = 2932, 2858, 2235, 2198, 1635, 1593 cm^{-1}. HRMS (ESI): calcd. for $C_{28}H_{37}IO_5$ [M + H]$^+$ 453.2636; found 453.2649.

1-(4-Methoxyphenyl)oct-2-yn-1-one (9b): [$PdCl_2(PPh_3)_2$] (300 mg, 0.4 mmol, 0.05 equiv.), H_2O (15 mL), Et_3N (3.5 mL, 25.5 mmol, 3 equiv.), and 1-heptyne (2.2 mL, 17.0 mmol, 2 equiv.) were added successively to a solution of 4-iodoanisole (2.0 g, 8.5 mmol, 1 equiv.) in CH_2Cl_2 (15 mL). Carbon monoxide was bubbled through the solution and the reaction was stirred for 24 h under an atmosphere of carbon monoxide (balloon filled with carbon monoxide) at room temperature. Water was added and then the mixture was extracted with ethyl acetate, the combined organic layers were dried with Na_2SO_4, filtered, and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (cyclohexane/ethyl acetate, 9:1) to give **9b** as a red oil (1.9 g, 96%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.07 (d, ^3J = 8.7 Hz, 2 H), 6.90 (d, ^3J = 8.7 Hz, 2 H), 3.82 (s, 3 H), 2.43 (t, ^3J = 7.2 Hz, 2 H), 1.63 (quint, ^3J = 7.2 Hz, 2 H), 1.46–1.27 (m, 4 H), 0.94 (t, ^3J = 7.2 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 176.8, 164.2, 131.8, 130.3, 113.6, 95.9, 79.6, 55.5, 31.0, 27.5, 22.1, 19.1, 13.8 ppm. Data are consistent with those reported in the literature.[15]

General Procedure for Cyclodehydration Conditions: Reactions were performed in a MiniBlock® XT Mettler Toledo reactor (24 positions).

Dinucleophile **4**–**7** (0.33 mmol, 3 equiv.) was added to a solution of **9a** (50 mg, 0.11 mmol, 1 equiv.) diluted in solvent (2 mL) before base (0.33 mmol, 3 equiv.) was added. The reaction mixtures were stirred at 50 °C and analyzed by APPI mass spectrometry.

Representative Procedure for APPI Mass Spectrometry Analyses: A sample of the crude mixture (9 μL) was added to a solution of MeOH/toluene (991 μL; 8:2) to give a final concentration of 5×10^{-4} M (based on starting material) and was then transferred to the mass spectrometer. The yields were evaluated by the ratio of the integral of the isotopic mass of the expected compound to the sum of the integrals of all detected compounds.

Mass spectrometer settings: Fragmentor voltage: 110 V. Capillary voltage: 1400 V. Drying gas flow: 5 L min^{-1}. Drying gas temperature: 250 °C. Nebulizer pressure: 250 psi. Mobile phase flow (methanol): 0.5 mL min^{-1}. Injection flow: 250 μL min^{-1}; time per run: 2 min; volume transferred into the mass spectrometer: 5 μL.

1-Methyl-5-pentyl-3-(4-{[5-(2,4,6-trimethoxyphenyl)pentyl]oxy}phenyl)-1*H*-pyrazole (10a): Light yellow solid; m.p. 67–69 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.69 (d, ^3J = 8.8 Hz, 2 H), 6.92 (d, ^3J = 8.8 Hz, 2 H), 6.26 (s, 1 H), 6.14 (s, 1 H), 3.98 (t, ^3J = 6.6 Hz, 2 H), 3.81 (s, 6 H), 3.79 (s, 6 H), 2.59 (t, ^3J = 7.4 Hz, 2 H), 1.84 (quint, ^3J = 6.6 Hz, 2 H), 1.68 (quint, ^3J = 7.4 Hz, 2 H), 1.54–1.50 (m, 4 H), 1.40–1.37 (m, 4 H), 0.94 (t, ^3J = 6.7 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 159.1, 158.8, 149.9, 144.5, 129.9, 126.5, 126.4, 114.5, 111.6, 100.9, 90.5, 68.15, 55.6, 55.3, 36.1, 31.5, 29.2, 28.2, 25.9, 25.7, 22.5, 22.3, 14.0 ppm. IR (neat): $\tilde{\nu}$ = 2928, 2856, 1610, 1596, 1495, 1455, 1432, 1249, 1149, 1138 cm^{-1}. HRMS (ESI): calcd. for $C_{29}H_{41}N_2O_4$ [M + H]$^+$ 481.3061; found 481.3076.

3-(4-Methoxyphenyl)-1-methyl-5-pentyl-1*H*-pyrazole (10b): Compound **4** (68 μL, 1.3 mmol, 3 equiv.) was added to a solution of **9b** (100 mg, 0.4 mmol, 1 equiv.) in CH_2Cl_2 (2 mL). The reaction mixture was stirred under reflux until the end of the reaction (2 d). Water was added and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried with Na_2SO_4, filtered, and evaporated under reduced pressure. Purification by column chromatography on silica gel (pentane/diethyl ether, 1:1) afforded the product as a mixture of regioisomers [**10b/10b′** (≈ 95:5) determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture] as an orange solid (105 mg, 93%); m.p. 40–42 °C. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 7.71 (d, ^3J = 8.8 Hz, 2 H), 6.92 (d, ^3J = 8.8 Hz, 2 H), 6.26 (s, 1 H), 3.83 (br. s, 6 H), 2.60 (t, ^3J = 7.6 Hz, 2 H), 1.64 (m, 2 H), 1.39–1.38 (m, 4 H), 0.93 (t, ^3J = 6.3 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 159.0, 149.6, 144.4, 129.8, 126.5, 113.8, 100.8, 55.1, 35.9, 31.3, 28.1, 25.5, 22.4, 13.9 ppm. IR (neat): $\tilde{\nu}$ = 2926, 2857, 1612, 1520, 1456, 1433, 1248 cm^{-1}. HRMS (ESI): calcd. for $C_{16}H_{23}N_2O$ [M + H]$^+$ 259,1805; found 259,1807.

5-(4-Methoxyphenyl)-1-methyl-3-pentyl-1*H*-pyrazole (10b′): Diagnostic signals: ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 7.33 (d, ^3J = 8.8 Hz, 2 H), 6.94 (d, ^3J = 8.8 Hz, 2 H), 6.06 (s, 1 H) ppm.

4-Pentyl-2-phenyl-6-(4-{[5-(2,4,6-trimethoxyphenyl)pentyl]oxy}-phenyl)pyrimidine (11a): White solid; m.p. 72–74 °C. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 8.60 (m, 2 H), 8.20 (d, ^3J = 8.5 Hz, 2 H), 7.51 (m, 3 H), 7.39 (s, 1 H), 7.03 (d, ^3J = 8.5 Hz, 2 H), 6.15 (s, 2 H), 4.05 (t, ^3J = 6.6 Hz, 2 H), 3.82 (s, 3 H), 3.81 (s, 6 H), 2.86 (t, ^3J = 7.6 Hz, 2 H), 2.62 (t, ^3J = 6.8 Hz, 2 H), 1.94–1.81 (m, 4 H), 1.55–1.27 (m, 8 H), 0.94 (t, ^3J = 6.8 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 171.3, 164.1, 163.3, 161.2, 159.2, 158.9, 138.5, 130.3, 129.6, 128.7, 128.4, 114.8, 112.5, 111.7, 90.6, 68.4, 55.7, 55.4, 38.3, 31.7, 29.2, 29.2, 28.7, 26.0, 22.6, 22.4, 14.1 ppm. IR (neat): $\tilde{\nu}$ = 2929, 2856, 1606, 1589, 1569, 1527, 1512, 1370, 1251, 1147, 1130 cm^{-1}. HRMS (ESI): calcd. for $C_{35}H_{43}N_2O_4$ [M + H]$^+$ 555.3217; found 555.3232.

4-(4-Methoxyphenyl)-6-pentyl-2-phenylpyrimidine (11b): Compound **5** (406 mg, 2.3 mmol, 3 equiv.) was added to a solution of **9b** (200 mg, 0.8 mmol, 1 equiv.) in THF/H_2O (1:1) (2 mL) followed by K_2CO_3 (356 mg, 2.5 mmol, 3 equiv.). The reaction mixture was stirred at 50 °C until the end of the reaction (2 d). Water was added and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried with Na_2SO_4, filtered, and evaporated under reduced pressure. Purification by column chromatography on silica gel (pentane/ethyl acetate, 8:2) afforded **11b** as a white solid (263 mg, 92%); m.p. 53–55 °C. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 8.60 (m, 2 H), 8.21 (d, ^3J = 8.6 Hz, 2 H), 7.50 (m, 3 H), 7.39 (s, 1 H), 7.04 (d, ^3J = 8.6 Hz, 2 H), 3.90 (s, 3 H), 2.86 (t, ^3J = 7.7 Hz, 2 H), 1.89–1.84 (m, 2 H), 1.45–1.40 (m, 4 H), 0.93 (t, ^3J = 6.5 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 171.8, 164.0, 163.17, 161.7, 138.5, 130.3, 129.8, 128.7, 128.4, 114.1, 112.5, 55.4, 38.2, 31.6, 28.6, 22.6, 14.1 ppm. IR (neat): $\tilde{\nu}$ = 2918, 2850, 1607, 1589, 1570, 1530, 1512, 1371, 1258, 1170 cm^{-1}. HRMS (ESI): calcd. for $C_{22}H_{25}N_2O$ [M + H]$^+$ 333.1961; found 333.1954.

5-Pentyl-7-(4-{[5-(2,4,6-trimethoxyphenyl)pentyl]oxy}phenyl)-pyrazolo[1,5-*a*]pyrimidine (12a): Waxy solid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.10 (d, ^3J = 2.4 Hz, 1 H), 8.02 (d, ^3J = 9.0 Hz, 2 H), 7.06 (d, ^3J = 7.04 Hz, 2 H), 6.75 (s, 1 H), 6.64 (d, ^3J = 2.4 Hz, 1 H), 6.14 (s, 2 H), 4.05 (t, ^3J = 6.5 Hz, 2 H), 3.81 (s, 3 H), 3.81 (s, 6 H), 2.60 (t, ^3J = 7.8 Hz, 2 H), 2.48 (t, ^3J = 7.1 Hz, 2 H), 1.90–1.75 (m, 4 H), 1.53–1.50 (m, 4 H), 1.44–1.34 (m, 4 H), 0.92 (t, ^3J

= 6.7 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 162.7, 161.5, 159.2, 158.9, 149.6, 146.4, 144.6, 131.0, 123.1, 114.7, 111.75, 106.9, 95.8, 90.6, 68.5, 55.8, 55.4, 38.5, 31.7, 29.8, 29.2, 29.0, 26.0, 22.6, 22.4, 14.1 ppm. IR (neat): $\tilde{\nu}$ = 2929, 2856, 1603, 1503, 1130 cm^{-1}. HRMS (ESI): calcd. for $C_{31}H_{40}N_3O_4$ [M + H]$^+$ 518.3013; found 518.3026.

7-(4-Methoxyphenyl)-5-pentylpyrazolo[1,5-*a*]pyrimidine (12b): A solution of **6** (108 mg, 1.3 mmol, 3 equiv.) in CH_2Cl_2 (1 mL) was added to a Schlenk tube containing **9b** (100 mg, 0.4 mmol, 1 equiv.) followed by K_2CO_3 (180 mg, 1.3 mmol, 3 equiv.). CH_2Cl_2 was evaporated by heating the reaction mixture at 65 °C. The reaction mixture was stirred at 65 °C until the end of the reaction (2 d). A saturated aqueous solution of NH_4Cl was added and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried with Na_2SO_4, filtered, and evaporated under reduced pressure. Purification by column chromatography on silica gel (pentane/diethyl ether, 7:3) afforded the products **12b** (107 mg, 83%) and **12b′** (13 mg, 10%); m.p. 52–54 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.10 (d, ^3J = 1.89 Hz, 1 H), 8.04 (d, ^3J = 8.6 Hz, 2 H), 7.07 (d, ^3J = 8.6 Hz, 2 H), 6.75 (s, 1 H), 6.64 (d, ^3J = 2.2 Hz, 1 H), 3.90 (s, 3 H), 2.85 (t, ^3J = 7.7 Hz, 2 H), 1.82 (quint, ^3J = 7.5 Hz, 2 H), 1.41–1.38 (m, 4 H), 0.92 (t, ^3J = 6.7 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 162.4, 161.4, 149.6, 145.8, 144.3, 130.7, 123.3, 113.8, 106.8, 95.6, 55.3, 38.4, 31.5, 28.7, 22.4, 13.9 ppm. IR (neat): $\tilde{\nu}$ = 2934, 2872, 2839, 1614, 1540, 1504, 1454, 1270, 1252, 1180, 1162 cm^{-1}. HRMS (ESI): calcd. for $C_{18}H_{22}N_3O$ [M + H]$^+$ 296.1757; found 296.1756.

5-(4-Methoxyphenyl)-7-pentylpyrazolo[1,5-*a*]pyrimidine (12b′): Waxy solid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.11 (d, ^3J = 2.4 Hz, 1 H), 8.06 (d, ^3J = 8.8 Hz, 2 H), 7.08 (s, 1 H), 7.03 (d, ^3J = 8.8 Hz, 2 H), 6.68 (d, ^3J = 2.4 Hz, 1 H), 6.64 (d, ^3J = 2.2 Hz, 1 H), 3.89 (s 3 H), 3.21 (t, ^3J = 7.8 Hz, 2 H), 1.93 (quint, ^3J = 7.6 Hz, 2 H), 1.53–1.40 (m, 4 H), 0.94 (t, ^3J = 7.2 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 161.5, 155.6, 149.7, 149.1, 144.7, 130.3, 128.9, 114.4, 103.3, 96.6, 55.5, 31.7, 30.8, 25.9, 22.5, 14.1 ppm. IR (neat): $\tilde{\nu}$ = 2953, 2926, 2854, 2872, 1601, 1577, 1551, 1513, 1419, 1377, 1257, 1234, 1172 cm^{-1}. HRMS (ESI): calcd. for $C_{18}H_{22}N_3O$ [M + H]$^+$ 296.1757; found 296.1756.

4-Pentyl-2-(4-{[5-(2,4,6-trimethoxyphenyl)pentyl]oxy}phenyl)-pyrimido[1,2-*a*]benzimidazole (13a): Orange solid; m.p. 130–132 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.18 (d, ^3J = 8.7 Hz, 2 H), 7.96 (d, ^3J = 8.1 Hz, 1 H), 7.82 (d, ^3J = 8.4 Hz, 1 H), 7.50 (t, ^3J = 7.6 Hz, 1 H), 7.30 (t, ^3J = 7.1 Hz, 1 H), 7.01 (s, 1 H), 6.95 (d, ^3J = 9.0 Hz, 2 H), 6.14 (s, 2 H), 3.99 (t, ^3J = 6.5 Hz, 2 H), 3.80 (s, 9 H), 3.24 (t, ^3J = 7.6 Hz, 2 H), 2.61 (t, ^3J = 7.0 Hz, 2 H), 1.93–1.83 (m, 4 H), 1.60–1.42 (m, 8 H), 0.98 (t, ^3J = 7.1 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 162.0, 160.5, 159.2, 158.9, 151.7, 145.5, 129.4, 128.9, 127.6, 125.6, 121.3, 120.1, 114.7, 114.6, 111.6, 102.5, 90.6, 68.4, 55.7, 55.4, 33.3, 31.5, 29.2, 29.1, 26.0, 22.5, 22.4, 14.1 ppm. IR (neat): $\tilde{\nu}$ = 2927, 2855, 2837, 1595, 1577, 1134 cm^{-1}. HRMS (ESI): calcd. for $C_{35}H_{42}N_3O_4$ [M + H]$^+$ 568.3170; found 568.3175.

2-(4-Methoxyphenyl)-4-pentylpyrimido[1,2-*a*]benzimidazole (13b): Compound **7** (173 mg, 1.3 mmol, 3 equiv.) was added to a solution of **9b** (100 mg, 0.4 mmol, 1 equiv.) in THF/H_2O (1:1) (2 mL). The reaction mixture was stirred at 50 °C until the end of the reaction (2 d). A saturated aqueous solution of NH_4Cl was added and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried with Na_2SO_4, filtered, and evaporated under reduced pressure. Purification by column chromatography on silica gel (diethyl ether/dichloromethane, 6:4) afforded **13b** as a yellow solid (88 mg, 78%); m.p. 136–138 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.10 (d, ^3J = 8.6 Hz, 2 H), 7.91 (d, ^3J = 7.9 Hz, 1 H), 7.71 (d, ^3J = 8.2 Hz, 1 H), 7.44 (t, ^3J = 7.6 Hz, 1 H), 7.20 (t, ^3J = 7.6 Hz, 1 H), 6.87 (s, 1 H), 6.87 (d, ^3J = 8.6 Hz, 2 H), 3.77 (s, 3 H), 3.11 (t, ^3J = 7.6 Hz, 2 H), 1.82 (quint, ^3J = 7.4 Hz, 2 H), 1.56–1.36 (m, 4 H), 0.95 (t, ^3J = 6.9 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 162.1, 160.2, 152.3, 151.7, 145.3, 129.2, 129.0, 127.5, 125.4, 121.2, 119.8, 114.6, 114.0, 102.1, 55.3, 33.1, 31.4, 25.8, 22.4, 14.0 ppm. IR (neat): $\tilde{\nu}$ = 2954, 2934, 2867, 1597, 1574, 1529, 1176 cm^{-1}. HRMS (ESI): calcd. for $C_{22}H_{24}N_3O$ [M + H]$^+$ 346.1914; found 346.1912.

Supporting Information (see footnote on the first page of this article): Copies of ^{1}H and ^{13}C NMR spectra of all compounds are provided.

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