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An Epiisopicropodophyllin Aza Analogue via Palladium-Catalyzed Pseudo-Domino Cyclization

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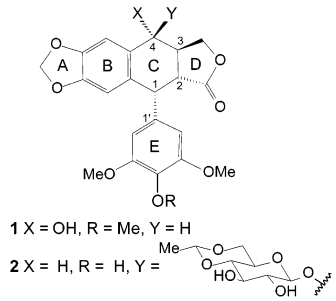
Abstract: A new aza analogue of epiisopicropodophyllin (the C-3 epimer of podophyllotoxin) has been synthesized exploiting two original strategic steps. Rings A/B and E are entered at an early stage via a cationic benzhydrylation process. A palladium-catalyzed pseudo-domino (Pd-PDOM) intramolecular process generates rings C/D in a single synthetic operation.

The synthesis of analogues of the well-known natural product podophyllotoxin **1** (Figure 1) and of the related etoposide **2** has attracted organic chemists since the antimitotic activity of the former compound and the antitumor properties of the latter were discovered.[1] In this context, a great deal of studies have been so far addressed to the synthesis of 2-azapodophyllotoxin analogues.[2] In fact, the presence of the amidic-type nitrogen atom at position 2 has been shown to remove the undesired trans-to-cis C/D-ring fusion epimerization, while enhancing D-ring stability. Indeed, hydrolytic D-ring opening is another major cause of concern since it also leads to drug inactivation.[3] To solve this problem, several D-ring modifications have been studied so as to take advantage of a nonhydrolyzable (and nonepimerizable) D-ring. Transformation of the podophyllotoxin or etoposide lactone D-ring into a trans-fused cyclopentane,[4] cyclopentanone,[3] tetrahydrofuran,[4,5] tetrahydrothiophene,[4] or δ-lactone[6] gave compounds less active than the parent



1 X = OH, R = Me, Y = H

2 X = H, R = H, Y =

FIGURE 1. Structures of podophyllotoxin **1** and etoposide (VP 16-213) **2**.

structures. Following a similar concept, Kadow and coworkers converted the lactone moiety of etoposide into a number of *N*-substituted lactam derivatives.[7] Although the synthetic protocol suffers from C-2 epimerization and the biological tests against P388 leukemia indicate inferior activity of these derivatives with respect to etoposide, podophyllotoxin- and etoposide-lactam derivatives may be regarded as interesting candidates.

The field of one-pot multistep processes is witnessing everincreasing attention and a consequent rapid evolution. Despite this evidence, a satisfactory conceptual picture covering transition metal-catalyzed domino reactions has, to the best of our knowledge, not been put forward yet. According to the commonly accepted definition by Tietze:[8] "*a domino reaction is a process involving two or more bond-forming transformations which take place under the same reaction conditions without additional reagents and catalysts, and in which the subsequent reactions result as a consequence of the functionality formed in the previous step*". On the other hand, when the above domino process is transition metal-catalyzed, three conceptually distinct categories may be further discriminated.[9] Thus, the process may either involve a single catalytic cycle, driven by a single catalytic system ("M") and featuring several distinct transition metal-catalyzed transformations, or be composed of sequential and mechanistically independent catalytic cycles, each one involving a simple catalytic transformation. Accord-

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(9) We warmly thank a referee for having provided us with the fundamental concepts enabling articulation of the principles underlying Figure 2.

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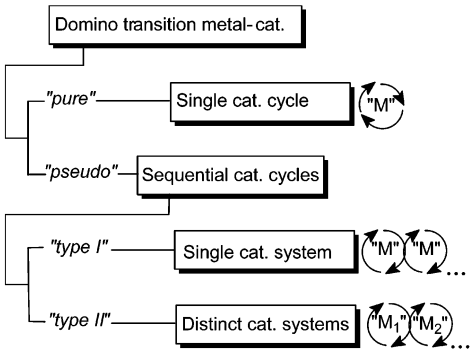
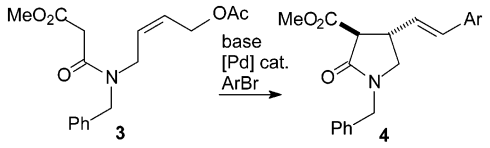


FIGURE 2. Classification of domino transition metal-catalyzed processes.

SCHEME 1



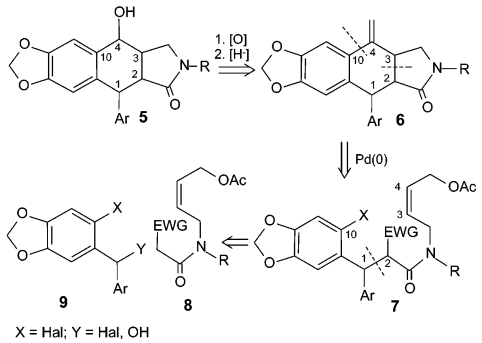
ing to the above consideration, we propose to distinguish and classify the two transition metal-catalyzed transformations as *pure-domino* (TM-DOM)[10] and *pseudo-domino* (TM-PDOM)[10] processes, respectively. Furthermore, the latter type of process may either involve a single "multipurpose" catalytic system ("M") sharing the sequential cycles (*type I*)[11] or call for mutually compatible catalytic systems of different nature ("M_1, M_2, ...") (*type II*). Figure 2 illustrates the above concept.

Although, according to the above notation, most of the known multistep transition metal-catalyzed reactions are TM-DOM processes,[12] examples of TM-PDOM *type I*[13,14] or TM-PDOM *type II*[15] transformations have been reported and are likely to receive increasing interest in the future.

We have recently developed a new Pd-PDOM *type I* process in which a single Pd-based catalytic system promotes two Pd-catalyzed processes in a one-pot procedure and in chronologically distinct order.[13] The first step consists of an intramolecular 5-*exo* cyclization of a stabilized acetamide anion onto an allylic acetate, whereas the latter one is an intermolecular regio- and stereoslective Heck arylation of the newly generated vinylpyrrolidinone (Scheme 1).[16]

Given the feasibility of such a sequence, we speculated that modification of the molecularity of the above strategy, from an "*intra−inter*" to an "*intra−intra*" type of process could offer an original access to lactam analogues of the podophyllotoxin family.[17]

SCHEME 2



The retrosynthetic disconnection of the podophyllotoxin lactam skeleton **5** leads first to the terminal alkene derivative **6** (Scheme 2). Such an intermediate may in turn be related to the open precursor **7** according to a 5-*exo* intramolecular allylic alkylation process followed by an intramolecular 6-*exo*-trig Heck reaction. Then, dissection at C-1/C-2 in **7** divides the molecule into the well-known unsaturated amide **8**[18] and the diarylmethanol derivative **9**.

The synthesis commenced with the preparation of the benzhydryl moiety. The required aromatic bromoaldehyde **10** (Scheme 3) was first secured in two steps via MnO_2 oxidation of piperonyl alcohol[19] followed by regioselective bromination of the resulting carbonyl derivative.[20] Addition of phenylmagnesium bromide to **10** in Et_2O gave the *o*-bromobenzhydrol **11** in 97% yield.[21] Treatment of this alcohol with PBr_3 in $CHCl_3$ afforded the benzhydrylbromide **12** in 94% yield.[22]

The reaction between the sodium enolate of **3** and the above dibromide **12** proved to be exceptionally inefficient, with only tiny amounts of the expected alkylated product **13** being isolated after 5 h at 60 °C in DMF.[23] An alternative approach was thus undertaken. Despite the virtual absence of similar examples in the literature,[24] direct addition of **3** to benzhydrol **11** in the presence of BF_3•OEt_2 gave the desired adduct **13** in quantitative yield as a mixture of the two possible diastereoisomers.[25,26]

(10) For the sake of straightforwardness we propose the intuitive acronyms TM-DOM and TM-PDOM to designate the transition metal-catalyzed domino and pseudo-domino processes, respectively, TM indicating the generic transition metal(s) involved in the catalysis.

(11) Of course, the real active catalysts driving each of the two sequential transformations may differ from one another, although deriving from the same catalytic system.

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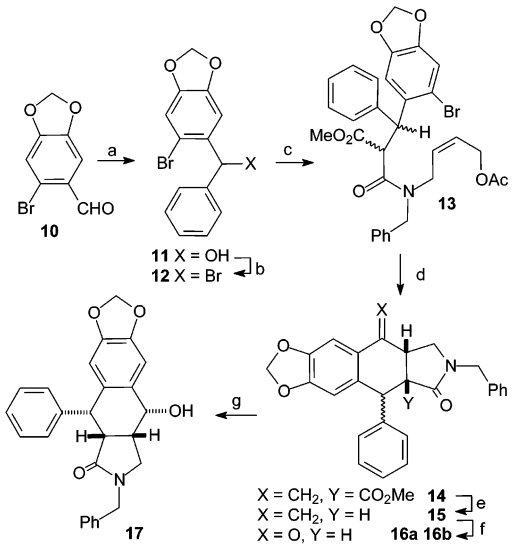
(22) Bream, J. B.; Schmutz, J. *Helv. Chim. Acta* **1977**, *60*, 2872−2880.

(23) The presence of the methylenedioxy bridge on the electrophile had a detrimental effect on the S_N2 substitution process. In fact, an analogous transformation using *o*-bromobenzhydryl bromide instead of **12** gave the desired alkylated product in high yield.

(24) Adams, J. T.; Levine, R.; Hauser, C. R. *Organic Syntheses*; Wiley: New York, 1955; Collect. Vol. III, pp 405−407.

SCHEME 3[a]



[a] Reagents and conditions: (a) PhMgBr, Et_2O, 0 °C → reflux, 10 min, 97%; (b) PBr_3, $CHCl_3$, rt, 22 h, 94%; (c) **3**, BF_3·OEt_2, rt, 15 min, quant.; (d) 10% $Pd(OAc)_2$, dppe, AcOK, DMF, 145 °C, 25 min, dr 75:25, 55%; (e) wet DMSO, NaCl, 160 °C, 5 h, 57%; (f) NMO, 5% $OsCl_3$, THF/H_2O, then $NaIO_4$, MeCOMe/H_2O, 91%; (g) $NaBH_4$, MeOH, rt, 30 min, quant.

Having successfully installed rings A/B and E, the crucial generation of C/D-rings was then tackled. Quite gratifyingly, treatment of **13** with a catalytic amount of $Pd(OAc)_2$ in the presence of dppe and AcOK,[27] in DMF at 145 °C, gave the desired tetracyclic structure **14** in 55% yield as a 75:25 mixture of two (out of four possible) diastereoisomers. Corollary cyclization experiments indicated that after 20 min at 85 °C the intermediate allylic alkylation product **13′** (not shown)[28] could be isolated in 79% yield, and its resubmission to the original reaction conditions gave again the final Heck product **14**. Careful NMR analysis suggested that both the isomers possessed a cis ring junction.[29] Heating **14** at 160 °C in the presence of NaCl in wet DMSO[30] gave three isomeric demethoxycarbonylated products in a 71:21:8 ratio. Chromatographic purification of the crude product allowed an easy removal of the third minor isomer **15′** (not shown) and isolation of the two major cis-fused diastereoisomers **15** as an inseparable 77:23 mixture. Given the reaction conditions of the decarboxylation reaction, preferential formation of the thermodynamically more stable cis-fused products was expected. Indeed, further transformations (see below) confirmed this expectation.

Unmasking of the C-4 carbonyl function was accomplished via osmium-catalyzed alkene cis-dihydroxylation followed by periodic oxidation of the generated diols. The resulting diastereomeric ketones **16a** and **16b** were

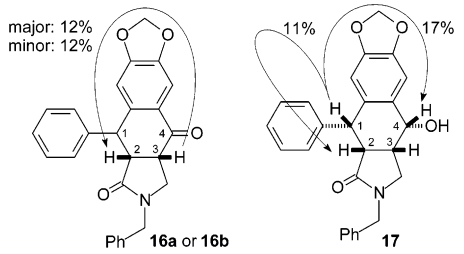


FIGURE 3. Selected NOE interactions observed in **16** and **17**.

obtained in 77:23 ratio and could be easily separated by column chromatography. The relevant coupling constants in both the isomers of **16**, as well as NOE experiments, suggest that the two epimers possess a cis C/D-ring junction and they differ by the relative stereochemistry between C-1 and C-2 (Figure 3).[31,32]

Finally, treatment of the major epimeric ketone **16a** with $NaBH_4$ in methanol afforded the crystalline carbinol **17** as a single diastereoisomer in quantitative yield.[31] A strong NOE value between H_1 and H_4 in the ^1H NMR spectrum clearly indicated a cis relationship between the phenyl ring and the hydroxyl group as well as their equatorial disposition. Furthermore, the coupling constant between H_2 and H_3 was suggestive of a cis ring junction.[32,33] Definitive stereochemical assignment came from the X-ray diffraction analysis of a single crystal of **17**. Inspection of the crystal structure[28] reveals also some remarkable conformational features. Owing to the cis fusion between the pyrrolidinone ring and the boat-shaped cyclohexane, the fused tetracyclic fragment appears as a bent ribbon. The boatlike shape of the cyclohexane is due to equatorial disposition of the hydroxyl and the phenyl ring. The E-ring is orthogonally disposed with respect to the cyclohexane ring, so as to minimize interaction with the neighboring atoms. Last, but not least, the *N*-benzyl group lies in the concave site of the tetracyclic moiety, in a "scorpion tail" disposition, with its phenyl ring almost bisecting the A/B/C/D scaffold.

Concerning the configurational assignment, the spectroscopic and crystallographic analyses unambiguously indicate that the newly synthesized aza-analogue **17** possesses the epiisopicropodopyllin stereochemistry (i.e., it is epimeric at C-3 with respect to podophyllotoxin).

Although cis ring junction in the podophyllolactone series is normally associated with low pharmacological activity, it should be pointed out that investigation on epiisopicropodophyllin has been so far hampered by its instability. In fact, this epimer is known to spontaneously rearrange to the more stable bridged isomeric form.[34] This is not the case for the aza-analogue **17** owing to the lower electrophilicity of the lactam with respect to the lactone function. Thus, the above synthesis represents the first entry to the epiisopicropodohyllin stereochemistry.

(25) Bisaro, F.; Prestat, G.; Vitale, M.; Poli, G. *Synlett* **2002**, 1823−1826.

(26) The diastereoisomeric ratio was not detectable by ^1H NMR owing to amide bond effect.

(27) Molar ratio $Pd(OAc)_2$:dppe:AcOK:**13** = 0.1:0.2:2.0:1.0.

(28) See Supporting Information.

(29) The value of the allylic coupling constants in both the diastereoisomers **14** was essentially zero. Previous studies in the laboratory indicated that such a feature is associated to cis junction.

(30) For reviews see: (a) Krapcho, A. P. *Synthesis* **1982**, 805−822. (b) Krapcho, A. P. *Synthesis* **1982**, 893−914.

(31) Brewer, C. F.; Loike, J. D.; Horwitz, S. B.; Sternlicht, H.; Gensler, W. J. *J. Med. Chem.* **1979**, *22*, 215−221.

(32) **16a** (major): $J_{1,2}$ = 6.64 Hz, $J_{2,3}$ = 9.92 Hz; **16b** (minor): $J_{1,2}$ = 1.44 Hz, $J_{2,3}$ = 7.32 Hz. **17**: $J_{1,2}$ = 4.56 Hz; $J_{2,3}$ = 9.16 Hz.

(33) Analogously, $NaBH_4$ reduction of the minor diastereoisomer **16b** gave quantitatively alcohol **17b** (structure not shown in the publication) as the only detectable epimer.

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In conclusion, the present study has allowed the synthesis of (±)-demethoxy epiisopicropodophyllin *N*-benzyl lactam. The crucial step consists of a Pd-PDOM *type I* doubly intramolecular process (allylic alkylation/Heck), which generates rings C/D in a single synthetic operation. Rings A/B and E are separately assembled and entered at an early stage via a new and efficient cationic benzhydrylation process. The synthesis is convergent and straightforward, entailing 10 sequential synthetic operations starting from 1,4-dihydroxy-2-butene with a 15% global yield. Future investigations will address the installation of the methoxylated E-ring and access to the different stereochemical manifolds, possibly in enantioselective versions. Biological activity tests for **17** and related derivatives will also be addressed.

Experimental Section

General Methods. All reactions were conducted under dried nitrogen or argon atmosphere using oven-dried glassware. For air- and/or water-sensitive reactions, glassware was flame-dried and then allowed to cool under argon or dried nitrogen atmosphere before use. All solvents were purified and distilled according to standard methods. Chromatographic purifications were conducted using 40−63 μm or 15−40 μm silica gel. All NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 (D_2O). Elemental analyses were carried out with accepted tolerance of ±0.3 units on carbon (C), hydrogen (H), and nitrogen (N). All compounds were isolated as oils unless otherwise specified, and their purities were determined to be >95% by NMR analysis. Compounds **14**−**17** are named according to podophyllotoxin numbering.

(±)-(1*R*,2*R*,3*S*)-12-Benzyl-2-methoxycarbonyl-4-methylene-6,7-methylenedioxy-1-phenyl-3-hydrobenzo[*f*]isoindol-13-one and (±)−(1*S*,2*R*,3*S*)-12-Benzyl-2-methoxycarbonyl-4-methylene-6,7-methylenedioxy-1-phenyl-3-hydrobenzo-[*f*]isoindol-13-one (14). To a solution of the acyclic precursor **13** (180 mg, 0.298 mmol) in dry DMF (2 mL), at 0 °C, under argon atmosphere was added NaH (60% dispersion in mineral oil) (13 mg, 0.328 mmol), and the solution was stirred at ambient temperature for 20 min. In a separate flask, $Pd(OAc)_2$ (6.6 mg, 0.0298 mmol) and dppe (24 mg, 0.0596 mmol) were dissolved in dry DMF (1 mL). After 20 min stirring at ambient temperature solid AcOK (58 mg, 0.596 mmol) was added to the thus formed Pd(0) complex. The previously generated enolate was then cannulated into the Pd(0) solution, and the resulting mixture was stirred at 145−147 °C for 25 min. A 25 wt % aqueous NH_4Cl solution (2 mL) was then added, and the aqueous phase was extracted with Et_2O (3 × 6 mL). The collected organic phases were dried, and the solvent was removed in a vacuum. Flash chromatography (hexanes/AcOEt, 75:25) gave the desired hydrobenzoisoindolone derivative **14** as an inseparable mixture of two diastereoisomers (75:25): pale yellow gum (55%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.36−7.13 and 6.87−6.84 (11H), 6.56 (s, 1H, 25%), 6.37 (m, 1H, 75%), 5.95 (AB system, 2H, 25%), 5.93 (AB system, 2H, 75%), 5.51 (s, 1H, 75% and s, 1H, 25%), 4.82 (part of AB system, 1H, 75%), 4.74 (d, 1H, J = 2.55 Hz, 25%), 4.68 (s, 1H, 75% and s, 1H, 25%), 4.66 (d, 1H, J = 1.53 Hz, 75%), 4.49 (part of AB system, 1H, 25%), 4.33 (part of AB system, 1H, 75%), 4.28 (part of AB system, 1H, 25%), 3.58 (s, 3H, 25%), 3.40−3.25 (3H, 75% and 2H, 25%), 3.37 (s, 3H, 75%), 3.23−3.19 (m, 1H, 25%). ^{13}C NMR ($CDCl_3$, 100 MHz, selected data): δ 46.45, 47.39, 47.63, 49.16, 49.79, 53.43, 52.84, 60.98, 62.10, 102.24, 102.36, 104.27, 104.56, 105.21, 105.86, 111.01, 111.48, 128.18, 128.59, 128.83, 128.91, 129.01, 129.52, 129.70, 129.82, 130.64, 132.65, 133.85, 134.08, 137.17, 137.37, 140.79, 141.10, 142.06, 147.87, 148.44, 149.01, 149.85, 169.34, 169.98, 171.47, 173.51. IR ($CDCl_3$): 3090, 3020, 2950, 2900, 1735, 1695 cm^{-1}. MS (CI − NH_3) m/z (%): 468 ($M^+ + H^+$), 485 ($M^+ + NH_4^+$). Anal. Calcd for $C_{29}H_{25}NO_5$: C, 74.50; H, 5.39; N, 3.00. Found: C, 74.36; H, 5.20; N, 2.88.

(±)-(1*R*,2*R*,3*R*)-12-Benzyl-6,7-methylenedioxy-4-methylene-1-phenyl-2,3-dihydrobenzo[*f*]isoindol-13-one and (±)-(1*R*,2*S*,3*S*)-12-Benzyl-6,7-methylenedioxy-4-methylene-1-phenyl-2,3-dihydrobenzo[*f*]isoindol-13-one (15), and (±)-(6,7-Methylenedioxy-4-methylene-1-phenyl-12-benzyl-2,3-dihydrobenzo[*f*]isoindol-1-one (15′) (unknown relative configuration, structure not shown in the publication). To a solution of the fused lactams **14** (0.226 g, 0.483 mmol), in DMSO (4 mL) and H_2O (20 μL), was added NaCl (56 mg, 0.966 mmol), and the resulting mixture was stirred at 160 °C for 5 h. After the mixture was cooled to ambient temperature, water was added (40 mL) and the solution was extracted with AcOEt (3 × 15 mL). The collected organic phases were dried, and the solvent was removed in a vacuum. ^{1}H NMR analysis of the crude product showed the presence of three diastereomeric decarboxylated lactams in a 71:21:8 ratio. Flash-chromatography (hexanes/AcOEt, 80:20) allowed isolation of the two major, inseparable, cis-fused diastereisomers **15** (49%, 74% considering the recovered unreacted starting material) and of the minor one **15′**, whose relative stereochemistry could not be assigned. **15**: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.28−7.10 and 6.90−6.66 (12H), 5.99 (AB system, 2H, 23%), 5.97 (AB system, 2H, 77%), 5.52 (d, 1H, 77%, J = 3.08 Hz), 5.24 (s, 1H, 23%), 4.89 (s, 1H, 23%), 4.86 (d, 1H, 77%, J = 2.56 Hz), 4.70 (d, 1H, 23%, J = 1.52 Hz), 4.62 (part of AB system, 1H, 23%), 4.54 (d, 1H, 77%, J = 6.08 Hz), 4.27 (part of AB system, 1H, 77%), 4.14 (part of AB system, 1H, 23%), 4.11 (part of AB system, 1H, 77%), 3.65 (dd, 1H, 23%, J = 9.64 Hz, J = 7.64 Hz), 3.55 (m, 1H, 77%), 3.38 (part of ABX system, 1H, 77%), 3.39−3.30 (1H, 77%, part of ABX system, 2H, 23%), 3.18 (dd, 1H, 77%, J = 10.16 Hz, J = 6.08 Hz), 2.99 (dd, 1H, 23%, J = 10.16 Hz, J = 2.04 Hz), 2.66 (part of AB system, 1H, 77%). ^{13}C NMR ($CDCl_3$, 100 MHz, selected data): δ 35.46, 36.07, 45.63, 46.34, 47.76, 48.63, 52.71, 54.35, 101.12, 101.26, 105.31, 105.75, 108.89, 111.31, 126.34, 126.94, 127.31, 127.41, 127.61, 127.83, 127.92, 128.20, 128.42, 128.56, 129.59, 130.16, 130.87, 131.07, 132.52, 135.72, 135.98, 139.97, 142.96, 144.01, 146.13, 147.49, 147.59, 148.20, 174.10, 174.18. IR ($CDCl_3$): 3075, 3010, 2960, 1685 cm^{-1}. MS (CI − NH_3) m/z (%): 410 ($M^+ + H^+$), 427 ($M^+ + NH_4^+$). Anal. Calcd for $C_{27}H_{23}NO_3$: C, 79.20; H, 5.66; N, 3.42. Found: C, 79.44; H, 5.73; N, 3.58. **15′**: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.37−7.07 (11H), 6.30 (s, 1H), 5.91 (AB system, 2H), 5.39 (d, 1H, J = 1.88 Hz), 4.72 (d, 1H, J = 2 Hz), 4.46 (AB system, 2H), 4.25 (d, 1H, J = 11.4 Hz), 3.41 (AB system, 2H), 2.94−2.89 (m, 1H), 2.69 (dd, 1H, J = 13.64 Hz, J = 11.4 Hz). MS (CI − NH_3) m/z (%): 410 ($M^+ + H^+$), 427 ($M^+ + NH_4^+$).

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Supporting Information Available: Experimental procedures and characterization data for the following compounds: piperonal, **10**, **11**, **12**, **13**, **13′**, **16a**, **16b**, **17**, and **17′**. X-ray ORTEP structure and crystallographic data for compound **17**. ^{1}H and ^{13}C NMR spectra for all previously unreported compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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