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Diastereoselective Synthesis of Polycyclic Acetal-Fused Pyrano[3,2-*c*]pyran-5(2*H*)-one Derivatives

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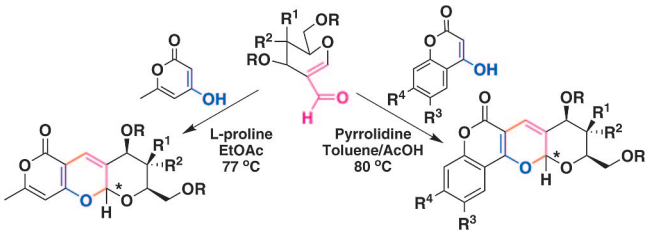

A facile and efficient diastereoselective one-pot synthesis of polycyclic acetal-fused pyrano[3,2-*c*]pyrane-5(2*H*)-one was achieved through the annulation reaction of 2-*C*-formyl glycals with various 4-hydroxycoumarins and 4-hydroxy-6-methyl-2*H*-pyran-2-one. The asymmetric induction was significantly influenced by the C-4 stereogenic center of 2-*C*-formyl glycals. The resulting polycyclic acetal-fused pyranopyrones demonstrated anticancer activities.

The syntheses of drug-like small molecules that specifically perturb the individual functions of gene products, enable the exploration of biological pathways in cells or organisms.[1] Further, bioactive compounds are widely used to modulate protein function and can serve as important leads for drug development.[2] Therefore, the development of an efficient route for the synthesis of a drug-like bioactive small molecule has been the research focus of medicinal/bioorganic chemists and chemical biologists.[3] Diversity-oriented synthesis (DOS) aims to populate the chemical space with skeletally and stereochemically diverse small molecules with high appending potentials and has been proven to be an essential tool for the discovery of bioactive small molecules.[4] In the DOS pathway, the incorporation of privileged substructures into novel core skeletons becomes imperative.[5] Coumarin or fused-pyrone derivatives are found in various natural bioactive and synthetic products as well as pharmaceutical agents (**A**−**D**, Figure 1).[6] They exhibit

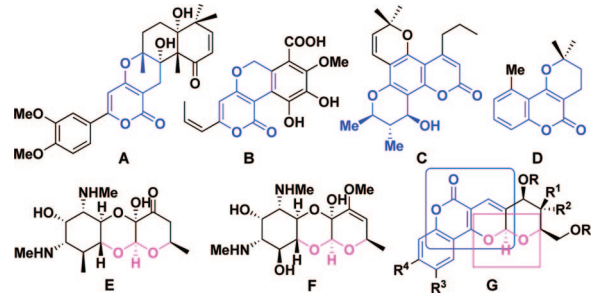

FIGURE 1. Bioactive small molecules with the pyranopyrone skeleton (**A**−**D**) and antibiotics with acetal-fused rings (**E** and **F**): (**A**) arisugacin A, a selective inhibitor of acetylcholinesterase; (**B**) cyathuscavins A, an antioxidant; (**C**) calanolide A, anti-HIV drug; (**D**) pterophyllin; (**E**, **F**) spectinomycin and acmimycin, antibiotics; and (**G**) our designed novel acetal-fused pyranopyrones.

antidiabetic, anti-Alzheimer, antitumor, anticoagulant, insecticidal, hypnotic, and antifungal properties, and inhibit the HIV protease.[6,7] Fused-acetal moieties are also present in a variety of biologically active natural products, i.e,. spectinomycin (**E**) and acmimycin (**F**).[8] Numerous literature reports regarding bioactivities of the fused acetal motif and coumarin/pyrone derivatives strongly support their values as privileged substructural moieties. In continuation of our research on DOS,[9] we designed and synthesized polycyclic acetal-fused pyrano[3,2-*c*]pyrane-5-(2*H*)-ones (pyranopyrones, **G**) derived from the hybrid structure of 4-hydroxycoumarin and 2-*C*-formylglycals for the discovery of novel therapeutic agents.

For the synthesis of polycyclic acetal-fused pyranopyrones, we identified 2-*C*-formyl galactal **1** as a key intermediate in the s-*cis* enal system that can be transformed to the desired acetal-fused pyranopyrone via an annulation reaction with 4-hydroxycoumarin **8**.[10] This annulation reaction involving 4-hydroxycoumarin and α,β-unsaturated ketone was first cited by Link in 1944[11] and studied in detail later by Moreno-Mañas

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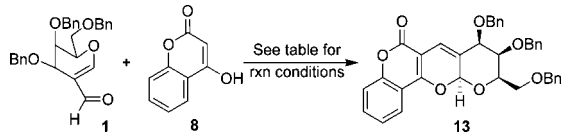
TABLE 1. Reaction Optimization for the Synthesis of 13



entry	reaction conditions[a]	dr (α:β)[b]	yield (%)
1[c]	EtOAc, 77 °C, 48 h	>99:1	29
2	**2a**, EtOAc, 77 °C, 20 h	>99:1	83
3	**2b**, EtOAc, 77 °C, 19 h	>99:1	82
4	**2c**, EtOAc, 77 °C, 19 h	>99:1	78
5	**2d**, EtOAc/AcOH (1:0.01), 77 °C, 3 h	>99:1	79
6	**2e**, EtOAc/AcOH (1:0.01), 77 °C, 6 h	>99:1	77
7	**2f**, EtOAc/AcOH (1:0.01), 77 °C, 7 h	>99:1	76
8	**2a**, EtOAc/AcOH (1:0.01), 77 °C, 17 h	>99:1	73
9	**2d**, CH_3CN/AcOH (1:0.01), 77 °C, 3 h	>99:1	50
10	**2d**, $CHCl_3$/AcOH (1:0.01), 77 °C, 4 h	>99:1	80
11[c]	**2d**, AcOH, 80 °C, 24 h	>99:1	50
12	**2d**, Toluene/AcOH (1:0.01), 80 °C, 3 h	>99:1	82

[a] 0.5 equiv of organocatalyst was used in each case. [b] Diastereomeric ratio (dr) was determined by crude ^{1}H NMR. [c] Reaction was not completed.

using 4-hydroxy-6-methylpyrane-2-one and (*E*)-2-butenal.[12] Since then, many research groups have explored and utilized this reaction for the synthesis of natural products and biologically relevant molecules.[13]

The annulation reaction of **1** with **8** was initially performed under simple refluxing condition in EtOAc without any additives or catalysts. As depicted in Table 1 (entry 1), polycyclic acetal-fused pyranopyrone **13** was obtained as a 29% yield with high diastereoselectivity along with the recovery of the starting material. The molecular structure of compound **13** was unambiguously established by 1D and 2D NMR (HMQC, HMBC, COSY, and NOE) experiments. The stereochemistry of newly generated chiral center was assigned by a strong NOE correlation between the acetal-fused methine proton (new chiral center) and predefined chiral protons (especially H-2′ and H-3′) of the sugar part in compound **13**. This suggested that the proton at the newly generated chiral center is in the same face as the methine proton at the sugar part in compound **13**. To optimize this reaction, we designed and tested a series of annulation conditions using various catalysts and solvent systems. The treatment of **1** with **8** in CH_2Cl_2 in the presence of Lewis acid ($TiCl_4$ or $InCl_3$) at 0 and 40 °C leads to the decomposition of **1** without yielding any desired product **13**. To enhance the reactivity of **1** through imine formation, secondary-amine-based organocatalysts were introduced (Figure 2).[14] After screening a set of reactions by using different concentrations of L-proline (**2a**) either at room temperature or reflux temperature, it was

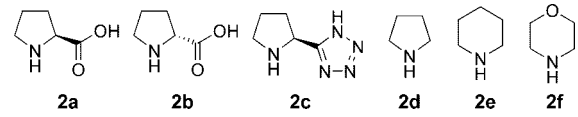


FIGURE 2. Organocatalysts.

found that the annulation of **1** with **8** in the presence of **2a** (0.5 equiv) in EtOAc at 77 °C affords **13** in good yield with excellent diastereoselectivity, though the reaction requires extended time for completion. When we tested the same transformation with D-proline (**2b**), we obtained the identical result of L-proline without the reduction of diastereoselectivity (Table 1, entry 3). In the case of more acidic tetrazole-based L-proline derivatives (**2c**), we did not observe any significant difference in the reaction rate (Table 1, entry 4).

Then, we turned our attention to simple achiral secondary amines as organocatalysts, but we observed that the annulation of **1** and **8** in the presence of pyrrolidine (**2d**) was halted at the imine formation of **1** and **2d** without forming any desired product after 6 h refluxing at 77 °C in EtOAc. At this juncture, we presumed that organocatalysts **2a**−**c** have an inherent proton source that helps accelerate the annulation reaction; however, **2d** requires an external proton source, i.e., acetic acid, for this transformation.[13f] To our pleasant surprise, **2d** can serve as an organocatalyst in the presence of 1% acetic acid to afford a single diastereomer **13** in fairly good yield (79%) with significant reduction of reaction time (Table 1, entry 5). Therefore, we concluded that the diastereoselectivity of the reaction leading to **13** is caused by substrate-control, not by reagent-control, because four different organocatalysts (**2a**−**d**) yield **13** with the same diastereoselectivity irrespective of chirality and acidity of organocatalysts (Table 1, entries 2−5). In our further optimization, piperidine (**2e**) and morpholine (**2f**) were found inferior compared to **2d** in terms of reaction time (Table 1, entries 6 and 7).

To study solvent effects, we screened toluene, acetonitrile, chloroform, methanol, and acetic acid in the presence of **2d** (Table 1, entries 9−12) and 1% acetic acid. In general, polar solvents, i.e., acetonitrile, acetic acid, and methanol, were not favorable because of the following reasons: acetonitrile and methanol provide poor yield of **13** (50% and 30%, respectively) and acetic acid causes an incomplete reaction even after a long time. In comparison, nonpolar solvents were generally better, and toluene was found to be the best solvent for this transformation (Table 1, entry 12).

The mechanism of this transformation can be postulated as shown in Figure 3: **2d** attacks the 2-*C*-formyl galactal **1** to form a carbinolamine (**I**), which undergoes the dehydration in the presence of a proton source (AcOH). The resulting iminium ion (**II**) is a better electrophile than **1** and undergoes nucleophilic *C*-1,2-addition with 4-hydroxycoumarin to afford **III**. Intermediate **III** rearranges to **IV**, which transforms into a conjugate intermediate **V** (1-oxatriene) with the regeneration of **2d** via β-elimination. Finally, **V** undergoes 6π-electron cyclization to afford the corresponding polycyclic acetal-fused pyranopyrone with excellent diastereoselectivity.[13d]

Having optimized reaction conditions, we investigated the scope of this transformation. As shown in Table 2 (entries 1−5), **1** was successfully coupled with various substituted 4-hydroxy-

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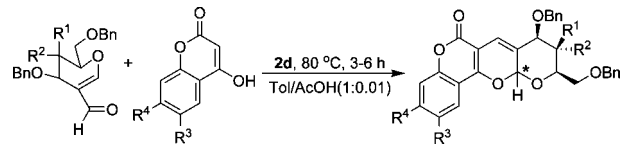
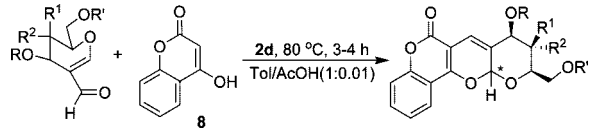
TABLE 2. Synthesis of Pyranopyrones



entry	enals	coumarin	R^1	R^2	R^3	R^4	dr[a] (α:β)	product	time/ yield (%)
1	**1**	**8**	OBn	H	H	H	>99:1	**13**	3 h/82
2	**1**	**9**	OBn	H	Cl	H	>99:1	**14**	5 h/82
3	**1**	**10**	OBn	H	Me	H	>99:1	**15**	4 h/82
4	**1**	**11**	OBn	H	Me	Me	>99:1	**16**	4 h/80
5	**1**	**12**	OBn	H	NO_2	H	>99:1	**17**	6 h/83
6[b]	**3**	**8**	H	OBn	H	H	55:45	**18a/18b**	18 h/87
7	**3**	**8**	H	OBn	H	H	55:45	**18a/18b**	4 h/84
8	**3**	**9**	H	OBn	Cl	H	57:43	**19a/19b**	6 h/85
9	**3**	**10**	H	OBn	Me	H	54:46	**20a/20b**	5 h/83
10	**3**	**11**	H	OBn	Me	Me	51:49	**21a/21b**	5 h/86
11	**3**	**12**	H	OBn	NO2	H	60:40	**22a/22b**	6 h/80

[a] Diastereomeric ratio (dr) was determined by crude ^{1}H NMR. [b] Reaction conditions: L-proline (0.5 equiv), EtOAc, 75 °C, 18 h.

TABLE 3. Reaction of Different Enals (1, 3−7) with 8



entry	enals	R	R^1	R^2	R′	dr[a] (α:β)	product	time/ yield (%)
1	**1**	Bn	OBn	H	Bn	>99:1	**13**	3 h/82
2	**3**	Bn	H	OBn	Bn	55:45	**18a/18b**	4 h/84
3	**4**	Me	OMe	H	Me	>99:1	**23**	4 h/50
4	**5**	Me	H	OMe	CPh_3	49:51	**24a/24b**	4 h/60
5	**6**	PMB	OPMB	H	PMB	>99:1	**25**	3 h/85
6	**7**	PMB	H	OPMB	PMB	51:49	**26a/26b**	3 h/88

[a] Diastereomeric ratio (dr) was determined by crude ^{1}H NMR.

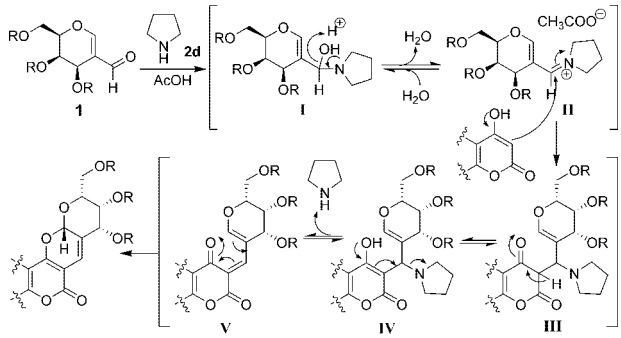


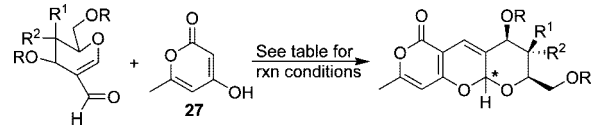
FIGURE 3. Plausible reaction mechanism.

coumarines (**8**−**12**) to afford respective products (**13**−**17**) in good yields with excellent diastereoselectivity. The substituents at the R^3 and R^4 positions on 4-hydroxycoumarin influenced neither the yield nor the reaction completion time. However, similar annulation reactions of 2-*C*-formyl glucal **3** afforded, unexpectedly, an epimeric mixture of polycyclic acetal-fused pyranopyrones **18a/18b** in good yields. The complete loss of asymmetric induction cannot be restored by using various solvents and chiral organocatalysts. In fact, the diastereoselectivity pattern in the annulations of **3** with **8** was identical when the organocatalyst used was L-proline **2a** or pyrrolidine **2d** (Table 2, entries 6 and 7). Similarly, different 4-hydroxycoumarines (**9**−**12**) were coupled with **3**, and their respective products (**19a/19b**−**22a/22b**) were obtained in good yields in the form of inseparable epimeric mixtures.

On the basis of these observations, we confirmed that diastereoselectivity is substrate-controlled and not reagent-controlled. Therefore, the drastic difference in the diastereoselectivity of the reactions might be caused by the structural difference between the C-4 stereogenic centers of **1** and **3**; the C-4 OBn group in the 1-oxatriene intermediate of **1** might interact sterically with the aromatic ring of 4-hydroxycoumarin, which results in conformational changes and a drastic difference in its diastereoselectivity. To confirm this hypothesis, tri-*O*-methyl-substituted 2-*C*-formyl galactal **4** was treated with **8** under the identical reaction conditions, and polycyclic acetal-fused pyranopyrone **23** was obtained as a single diastereomer. In contrast, the annulation of its glucal derivative **5** with **8** afforded an epimeric mixture of the corresponding products **24a/24b** (Table 3, entries 3 and 4). Similar diastereoselectivity patterns were observed in tri-*O*-*p*-methoxybenzyl (PMB)-protected **6** and its glucal derivative **7** with **8** (Table 3, entries 5 and 6). This pattern indicates that the C-4 stereogenic center itself plays a striking role in the stabilization of different conformers of **1** and **3**, which might lead to the difference in diastereoselectivity.[15a] On the basis of our calculations, the energy difference between galactal-derived pyranopyrones was $\Delta E = 3.97$ kcal/mol, whereas that of glucal-derived pyranopyrones was $\Delta E = 1.24$ kcal/mol,[15b] which can suggest a potential rationalization of the observed diastereoselectivity via thermodynamic equilibrium.[15b]

After the synthesis of tetracyclic acetal-fused pyranopyrones, we turned our attention to the synthesis of tricyclic acetal-fused pyranopyrones.[13f] In fact, it requires extended reaction time

TABLE 4. Reaction of Different Enals with 27



entry	enals	R^1	R^2	R	reaction conditions	product	dr[a] (α:β)	yield (%)
1	**1**	OBn	H	Bn	**2a**, EtOAc 77 °C, 20 h	**28**	>99:1	77
2	**1**	OBn	H	Bn	**2d**, toluene/AcOH (1:0.01), 80 °C, 21 h	**28**	>99:1	37
3	**1**	OBn	H	Bn	**2d**, EtOAc/AcOH (1:0.01) 77 °C, 22 h	**28**	>99:1	80
4	**3**	H	OBn	Bn	**2a**, EtOAc 77 °C, 22 h	**29a/29b**	51:49	80
5	**3**	H	OBn	Bn	**2d**, EtOAc/AcOH (1:0.01) 77 °C, 22 h	**29a/29b**	51:49	77
6	**6**	OPMB	H	PMB	**2a**, EtOAc 77 °C, 21 h	**30**	>99:1	88
7	**7**	H	OPMB	PMB	**2a**, EtOAc 77 °C, 20 h	**31a/31b**	52:48	87

[a] Diastereomeric ratio (dr) was determined by crude ^{1}H NMR.

when 4-hydroxy-6-methylpyran-2*H*-one **27** was subjected to the annulation with 2-*C*-formyl glycals (**1** and **3**) and EtOAc was a better solvent than toluene for these substrates (Table 4, entries 2 and 3). In the case of **1**, both L-proline **2a** and pyrrolidine **2d** served as good organocatalysts with similar reaction rates and afforded the desired tricyclic product **28** in good yields with excellent diastereoselectivity (Table 4, entries 1 and 3). However, of all the reaction conditions examined in our study, the treatment of **3** with **27** only afforded a diastereomeric mixture of tricyclic products **29a/29b** in an almost 1:1 ratio.

The resulting tetra- and tricyclic acetal-fused pyranopyrones were screened for their anticancer activities against three different cancer cell lines. As shown in SI Table 2, tetracyclic compounds **13**−**15** and **17** showed antiproliferative activity (IC_{50}) at micromolar concentrations. Further lead optimization of active compounds is currently in progress.

In summary, we have developed an efficient one-step synthetic protocol for the synthesis of polycyclic acetal-fused pyranopyrones. The acetal-fused pyranopyrones were designed to encompass stereochemically enriched carbohydrate skeletons. This sugar part can also be further modified and diversified to enhance their biological activities. Subsequently, we demonstrated that some of these pyranopyrones possess anticancer activities at micromolar levels. The complete library realization of these polycyclic acetal-fused pyranopyrones with DOS and their further biological evaluation will be reported in due course.

Experimental Section

Synthesis of Compound 13. To a stirred solution of 2-*C*-formyl galactal **1** (110 mg, 0.250 mmol) in 5 mL of toluene with 3 Å molecular sieves were added 8.9 mg of pyrrolidine (0.5 equiv) and 50 μL of AcOH, followed by the addition of 4-hydroxycoumarin **8** (48.6 mg, 0.30 mmol). The resulting mixture was heated at 80 °C, and the reaction completion was monitored by the consumption of 2-*C*-formyl galactal **1**. The product mixture was cooled to room temperature, and the reaction was quenched by the addition of $NaHCO_3$ (8 mL). The organic layer was separated, and the aqueous layer was extracted by EtOAc (3 × 5 mL). The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4. The crude product was purified by silica gel flash column chromatography to obtain the desired product **13** (120 mg) in 82% yield as an amorphous solid. R_f 0.40 (3:7 = acetone:hexanes, v/v); $[\alpha]^{28}_D$ −285.05 (*c* 0.453, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84 (dd, *J* = 8.0 and 1.5 Hz, 1H), 7.48 (dt, *J* = 8.0 and 1.5 Hz, 1H), 7.38−7.23 (m, 17H), 7.01 (d, *J* = 1.5 Hz, 1H), 6.08 (s, 1H), 4.93 (d, *J* = 11.5 Hz, 1H), 4.81 (d, *J* = 12.0 Hz, 1H), 4.66 (d, *J* = 12.0 Hz, 1H), 4.61 (d, *J* = 13.0 Hz, 1H), 4.47 (d, *J* = 11.5 Hz, 1H), 4.40 (d, *J* = 11.5 Hz, 1H), 4.14 (t, *J* = 2.0 Hz, 1H), 3.98 (d, *J* = 1.5 Hz, 1H), 3.85 (t, *J* = 6.5 Hz, 1H), 3.61 (dd, *J* = 9.5 and 6.0 Hz, 1H), 3.51 (dd, *J* = 9.5 and 6.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.8, 156.4, 152.9, 138.3, 137.9, 137.7, 132.4, 128.9, 128.8, 128.7, 128.4, 128.2, 128.1, 127.9, 127.6, 126.9, 124.4, 123.0, 116.9, 114.8, 112.8, 99.8, 97.1, 79.6, 76.6, 75.4, 74.6, 73.8, 71.9, 68.9; FAB HRMS *m/z* calcd for $C_{37}H_{32}O_7$ $[M + H]^+$ 589.2226, found 589.2225.

Synthesis of Compound 28. To a stirred solution of 2-*C*-formyl galactal **1** (110 mg, 0.250 mmol) in 5 mL of dry EtOAc with 3 Å molecular sieves was added L-proline (0.5 equiv) or pyrrolidine (0.5 equiv) with 50 μL of AcOH, followed by the addition of 4-hydroxy-6-methyl-2*H*-pyrane-2-one **27** (63 mg, 0.50 mmol). The resulting mixture was heated at 77 °C, and the reaction completion was monitored by the consumption of 2-*C*-formyl galactal **1**. Compound **27** was added in four installments. The product mixture was cooled to room temperature, and the reaction was quenched by adding $NaHCO_3$ (8 mL). The organic layer was separated, and the aqueous layer was extracted by EtOAc (3 × 5 mL). The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4. The crude product was purified by silica gel flash column chromatography to obtain the desired product **28** (110 mg) in 80% yield as an amorphous solid. R_f 0.45 (2:3 = acetone: hexanes, v/v); $[\alpha]^{28}_D$ −42.87 (*c* 0.333, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37−7.23 (m, 15H), 6.87 (d, *J* = 2.0 Hz, 1H), 5.90 (s, 1H), 5.87 (s, 1H), 4.92 (d, *J* = 12.0 Hz, 1H), 4.77 (d, *J* = 12.0 Hz, 1H), 4.65 (d, *J* = 12.0 Hz, 1H), 4.57 (d, *J* = 12.0 Hz, 1H), 4.46 (d, *J* = 12.0 Hz, 1H), 4.38 (d, *J* = 12.0 Hz, 1H), 4.06 (br s, 1H), 3.94 (d, *J* = 2.0 Hz, 1H), 3.76 (t, *J* = 6.0 Hz, 1H), 3.58 (dd, *J* = 9.5 and 5.5 Hz, 1H), 3.50 (dd, *J* = 9.5 and 6.5 Hz, 1H), 2.21 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.4, 162.3, 161.5, 138.4, 137.9, 137.8, 128.8, 128.6, 128.4, 128.2, 128.1, 128.0, 127.9, 127.5, 125.3, 112.4, 99.7, 97.6, 97.0, 79.6, 76.3, 75.3, 74.5, 73.8, 71.9, 68.8, 20.3; FAB HRMS *m/z* calcd for $C_{34}H_{32}O_7$ $[M + H]^+$ 553.2226, found 553.2222.

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Supporting Information Available: Experimental procedures, complete spectroscopic data, and NOE experiments along with copies of ^{1}H and ^{13}C NMR spectra of all compounds **13**−**31**. This material is available free of charge via the Internet at http://pubs.acs.org.

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