Determination of Absolute Configurations of Carbinols of Annonaceous Acetogenins with 2-Naphthylmethoxyacetic Acid Esters

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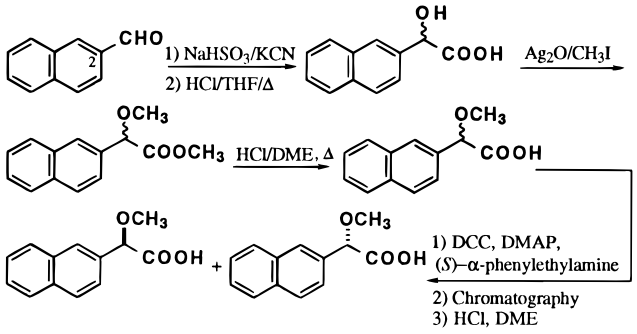
Structural elucidation of absolute configurations of the stereogenic centers of acetogenins of Annonaceae was performed using the modified Mosher's method. Thus, by replacing MTPA (methoxytrifluoromethylphenylacetic acid) by 2-NMA (naphthylmethoxyacetic acid), we were able to determine the absolute configuration of the stereogenic centers of rolliniastatin-2 by simple analysis of the ^{1}H NMR spectra recorded at 400 MHz. Indeed, by comparing the differences of chemical shifts between the MTPA esters with those obtained with 2-NMA esters, we showed that we could take advantage of the long-range anisotropic effect of the naphthyl ring for the elucidation of the unsymmetrical systems.

Introduction

Acetogenins of Annonaceae have been isolated so far only from several species of this botanical family, and because of their puzzling bioactivities (e.g. cytotoxic, antitumor, antiparasitic, insecticide, immunosuppressive), they have attracted the attention of many chemists and biologists.[1] Since the first isolation of uvaricin in 1982,[2] extraction and purification procedures as well as structural elucidations have became more straightforward. However, the determination of absolute configurations of the carbinols present in the annonaceous acetogenins remains the most challenging task in the structural elucidation of these natural products. To date, the best way is to use Mosher's ester method,[3] which has been applied to the acetogenins with some limited success.[1,4,5] This method consists of the comparison of the ^{19}F and ^{1}H NMR high-field spectra of the secondary alcohols derivatized as (*R*)- and (*S*)-2-methoxy-2-phenyl-2-(trifluoromethyl)acetates (MTPA). The difference of the chemical shifts of the diastereomers ($\Delta\delta_H = \delta_S - \delta_R$) indicates whether the alcohol is (*R*) or (*S*) based on the established conformational models.[3,6] Sometimes, however, specially in the case of carbinol isolated on the long aliphatic chain, these chemical shifts differ by 0.01 ppm or less, making the interpretation of the data difficult and unreliable.[1] A recent publication has shown furthermore that methoxyphenylacetic esters (MPA) as well as methoxyarylacetic esters were superior to the MTPA esters.[7] Therefore, we wish to report our findings concerning the use of 2-naphthylmethoxyacetic esters for the determination of the absolute configuration of carbinolic stereogenic centers of several acetogenins and to compare our results with those obtained with MTPA esters.

Scheme 1. Synthesis of (*R*)- and (*S*)-α-Methoxy-α-(2-naphthyl)acetic Acid



Results and Discussion

The use of 2-NMA esters and related 2-arylmethoxyacetic esters for absolute configuration determinations was developed simultaneously by several teams[8,9,10] and was shown to be more reliable than the usual method

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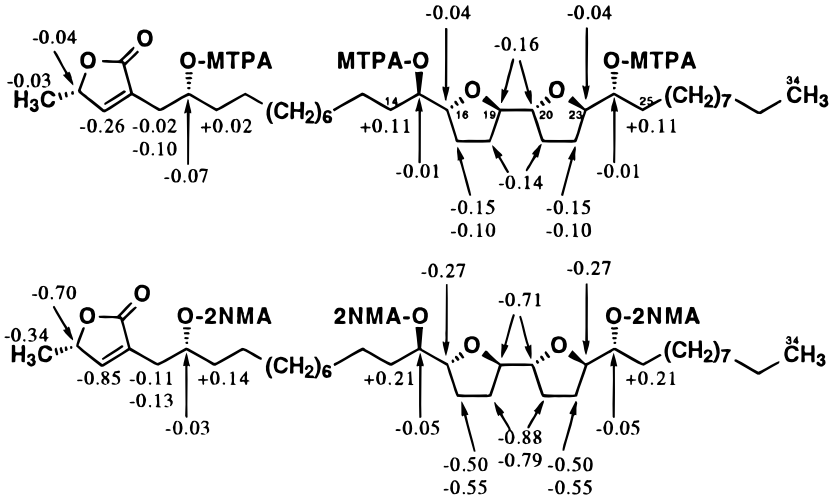
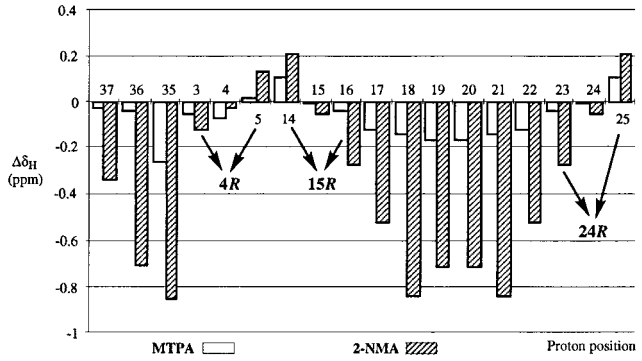
Scheme 2. $\Delta\delta_H$ of Per-MTPA and Per-2-NMA Esters of Asimicin (ref 4 and this work)



Scheme 3. Comparison of MTPA vs 2-NMA Esters of Asimicin



with MTPA esters. For our study, pure (*R*)- and (*S*)-2-NMA acids were prepared following Pohl's[11] and Latypov's[12] methods with some modifications. Indeed, in our hands we found that the desired acids were best obtained from the cyanohydrin of the corresponding 2-naphthaldehyde, followed by acid hydrolysis. The racemic hydroxy acid was then methylated by treatment with silver oxide and methyl iodide to afford the methyl α-methoxy-α-(2-naphthyl)acetate. Then after acidic hydrolysis, the racemic mixture of the arylmethoxyacetic acids was resolved through the formation of the amides from (*S*)-α-phenylethylamine and then separation by flash chromatography of the two diastereomers and acid hydrolysis to give pure (*R*)- and (*S*)-2-naphthylmethoxyacetic acids (Scheme 1). The absolute configurations of both acids were acertained by comparisons with the rotatory powers and by NMR analyses after derivatization with (−)-menthol. ^{1}H chemical shifts of 2-NMA menthol esters were in agreement with those described by Latypov,[7] and $\Delta\delta_H$ between the (*R*)- and (*S*)-esters of (−)-menthol were larger than in the case of MPA and MTPA menthol esters. These larger differences may be explained by the existence of a major rotamer with an sp conformation, whereas in the MTPA esters of menthol, three major rotamers with the lowest configurational energy exist, having opposite effects.[7] Furthermore, the anisotropic effect is more important with the naphthyl ring than with the phenyl ring.

We then derivatized asimicin as its per-2-NMA esters and analyzed by ^{1}H NMR the $\Delta\delta_H = \delta_R - \delta_S$ of several characteristic hydrogens (the difference must be inverted because of the inverted priority order compare to MTPA esters[13]). Schemes 2 and 3 summarize the $\Delta\delta_H$ values observed with MTPA and those with 2-NMA. These values are between 2 and 17 times larger in the case of 2-NMA esters than with MTPA, which allowed us to confirm the 4*R*,15*R*,16*R*,19*R*,20*R*,23*R*,24*R* absolute configurations of asimicin without ambiguity, following the rules established by Trost[6] and Latypov.[12]

In the case of squamocin, which possess threo/trans/threo/trans/erythro relative configuration, no details on the ^{1}H NMR studies were available in the literature, since its relative configuration was determined by X-ray[14] and the C28 absolute configuration was established as (*S*) by examining the $\Delta\delta_H$ of the terminal methyl of the per-MTPA esters ($\Delta\delta_H = -0.013$ ppm).[15] However, this very low difference is close to the experimental error. With the per-2-NMA esters of squamocin this value is now −0.15 ppm (10 times larger) and allows us to confirm the C28 (*S*) configuration. On the other hand, the positive value observed for $\Delta\delta_{H14}$ is in accord with the (*R*) absolute configuration of C15. We have shown by HOHAHA (2D homonuclear−Hartmann−Hahn) that the erythro configuration was settled between carbinols C23 and C24 (since C24 was connected to C28). Concerning its absolute configuration, we observed a positive value at C23 and a very low and positive value at C25, which could be explained by the additive effects of the 2-NMA esters. Nevertheless, the negative and high value for $\Delta\delta_{H28}$ (−0.32 ppm) is too important to be only due to a diastereomeric effect of the naphthyl group in the C28 position, suggesting an anisotropic effect of a close 2-NMA group. The 15-(2-NMA) group is too far away from the proton H28 to assert any significant influence on it. The $\Delta\delta_{H28}$ is dominated by the 24-(2-NMA) group and thus the negative value indicates that the configuration at C24 is (*S*). The 15*R*,16*R*,19*R*,20*R*,23*R*,24*S*,28*S*

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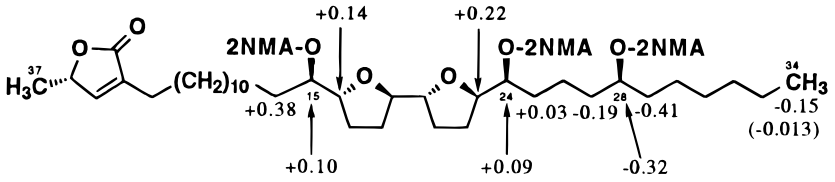
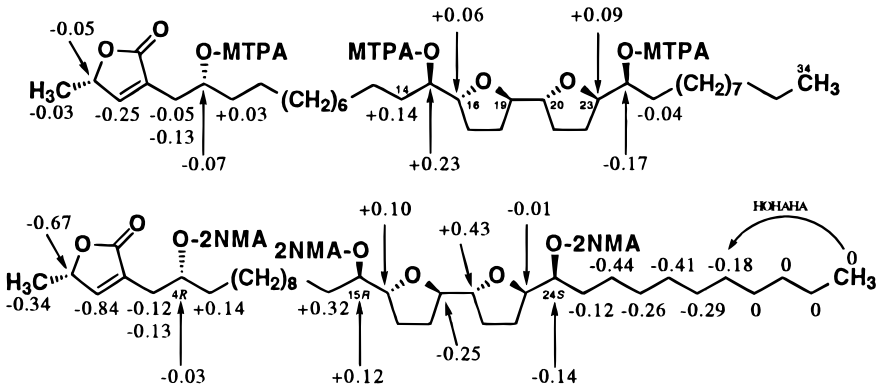
Scheme 4. $\Delta\delta_H$ of Per-2-NMA Esters of Squamocin (value in brackets, MTPA ester)



Scheme 5. $\Delta\delta$H of Per-MTPA and Per-2-NMA Esters of Rolliniastatin-2



may be then attributed to squamocin. It is noteworthy that the low, positive value observed for $\Delta\delta_{H16}$ may be explained by the additive effects of the NMA at the C24 position.

The case of rolliniastatin-2 (identical to bullatacin[1]) was even more interesting since its relative configuration was reported as threo/trans/threo/trans/erythro. However, the directionality of the nonsymmetric system remained questionable and the erythro position could be between C15 and C16 or C23 and C24.[16] Because of the lack of function near the hydroxyls at C15 and/or C24, HOHAHA experiments were useless. Thus after derivatization of rolliniastatin-2 as its per-2-NMA esters, it was possible to attribute six methylenes in the proximity of one of the hydroxyls (C15 and/or C24). Then, after the HOHAHA experiment we found a connectivity between the methyl terminal and one of the these six methylenes and thus could connect the hydroxyl at the C24 with the (*S*) absolute configuration (because of the negative sign of $\Delta\delta_{H25-H30}$). Then by comparing the chemical shift of the H24 with those of squamocin and asimicin, we could conclude that this corresponds to the chemical shift of an ester with an erythro configuration (5.02 vs 4.85 ppm for both the (*S*)-2-NMA esters of the threo counterparts). So the 2-NMA esters allowed us to attribute both the direction of the *relative configuration* and the *absolute configurations* without ambiguity. It is noteworthy that again the values with 2-NMA esters are much larger than when MTPA esters are used (Scheme 5).

In conclusion, the use of 2-NMA esters allows one to attribute the absolute configurations of several carbinolic of annonaceous acetogenins, and in some cases the position of the erythro relationship. Differences of chemical shifts are most of the times larger than those obtained with MTPA esters[4,15,17], and the (i) long-range anisotropic effect and (ii) additive effects of naphthyl rings allowed these attributions without ambiguity. The procedure is simple to settle and does not require preparation of mono derivatives in minute amounts, as in the case of MTPA esters.

Experimental Section

Optically pure α-methoxy-α-(2-naphthyl)acetic acids were obtained from commercial 2-naphthaldehyde after preparation of the corresponding cyanohydrin,[11,16] hydrolysis, methylation, and flash chromatography separation of the corresponding amides from (*S*)-α-phenylethylamine [hexane/EtOAc 70/30 v/v; R_f (*R*,*S*)-amide 0.27, R_f (*S*,*S*)-amide 0.37], followed by acid hydrolysis.

(−)-(*R*)-α-Methoxy-α-(2-naphthyl)acetic acid: $[\alpha]_D$ = −124 (*c* 0.32, MeOH) (lit.[12] −120.8 (*c* 0.0015, EtOH), (lit.[8] −138.7 (*c* 0.35, MeOH).

(+)-(*S*)-α-Methoxy-α-(2-naphthyl)acetic acid: $[\alpha]_D$ = +124 (*c* 0.32, MeOH) (lit.[12] +120 (*c* 0.005, EtOH), (lit.[8] +100.5 (*c* 0.63, MeOH).

General. Esters were prepared in $CHCl_3$ by treatment of acetogenins (3−5 mg) with the corresponding acid in the presence of DCC and catalytic DMAP, followed by purification by column chromatography on silica gel (Kieselgel 60H, Merck) with hexane/EtOAc (80/20, v/v), to afford the corresponding esters in 55−77% typical yields, as colorless oils.

NMR Experiments. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM 400 spectrometer. Chemical shifts were expressed in ppm with $CHCl_3$ as internal reference. Unambiguous attributions were confirmed by the following 2D experiments. 1D ^{1}H NMR: size, 16 K; pulse length, 5 μs; aquisitions, 32 or 64. 2D COSY-DQF: sequence, D_1−90°−t_1−90°−t_2; relaxation delay, D_1 = 1 s; 90° pulse for 5 μs. 2D Homonuclear−Hartmann−Hahn (HOHAHA): sequence, D_1−90°−mixing time; D_1 = 1 s; 90° pulse for 5 μs; mixing time, 64−80 ms.

Per-(*R*)-2-NMA Esters of Asimicin. ^{1}H NMR (δ ppm, $CDCl_3$): 0.77 (d, J = 6.8 Hz, 3H, CH_3-37), 0.78 (m, 2H, CH-18a and CH-21a), 0.88 (t, J = 6.8 Hz, 3H, CH_3-34), 0.90 (m, 4H, CH-18b, CH-21b, CH-17a, CH-22a), 1.22 (m, 28H), 1.31 (m, 4H, CH_2-13 and CH_2-26), 1.33 (m, 2H, CH-17b, CH-22b), 1.60 (m, 4H, CH_2-14 and CH_2-25), 1.62 (m, 2H, CH_2-5), 2.41 (ddd, J = 5.7, J' = J'' = 1.5 Hz, 2H, CH_2-3), 3.08 (ddd, J = J' = 5.8, J'' = 10.2 Hz, 2H, CH-19 and CH-20), 3.44 (s, 6H, 2(OCH_3)), 3.45 (s, 3H, OCH_3), 3.66 (ddd, J = 4.1, J' = 7.3, J'' = 10.3 Hz, 2H, CH-16 and CH-23), 3.95 (dq, J = 1.6, J' = 6.8 Hz, 1H, CH-36), 4.81 (ddd, J = 4.1, J' = 4.4, J'' = 9.0 Hz, 2H, CH-15 and CH-24), 4.900 (s, 1H, $CHOCH_3$), 4.905 (s, 1H,

(16) However, Rieser prepared the two mono MTPA esters and was able to attribute the erythro relative configuration between C23 and C24.[4]

(17) Added in proof: Gonzalez, M. C.; Lavaud, C.; Gallardo, T.; Zafra-Polo, M. C.; Cortes, D. *Tetrahedron* **1998**, *54*, 6079−6088.

$CHOCH_3$), 4.910 (s, 1H, $CHOCH_3$), 5.10 (dddd, $J = J' = J'' = 5.8$, $J''' = 11.5$ Hz, 1H, CH-4), 5.81 (q, $J = 1.5$ Hz, 1H, CH-35), 7.41−7.92 (m, 21H, aromatic).

Per-(*S*)-2-NMA Esters of Asimicin. ^{1}H NMR (δ ppm, $CDCl_3$): 0.88 (t, $J = 7.0$ Hz, 3H, CH_3-34), 1.11 (d, $J = 6.5$ Hz, 3H, CH_3-37), 1.30 (m, 32H), 1.40 (m, 4H, CH_2-14 and CH_2-25), 1.46 (m, 2H, CH-17a and CH-22a), 1.48 (m, 2H, CH_2-5), 1.57 (m, 2H, CH-18a and CH-21a), 1.78 (m, 2H, CH-18b and CH-21b), 1.84 (m, 2H, CH-17b and CH-22b), 2.52 (ddd, $J = 3.6$, $J' = J'' = 1.8$ Hz, 1H, CH-3a), 2.54 (ddd, $J = 7.4$, $J' = J'' = 1.6$ Hz, 1H, CH-3b), 3.45 (s, 3H, OCH_3), 3.47 (s, 3H, OCH_3), 3.48 (s, 3H, OCH_3), 3.80 (ddd, $J = J' = J'' = 5.7$ Hz, 2H, CH-19 and CH-20), 3.93 (ddd, $J = 6.4$, $J' = J'' = 2.0$ Hz, 2H, CH-16 and CH-23), 4.65 (dq, $J = 6.8$, $J' = 1.6$ Hz, 1H, CH-36), 4.85 (m, 2H, CH-15 and CH-24), 4.944 (s, 1H, $CHOCH_3$), 4.951 (s, 1H, $CHOCH_3$), 4.954 (s, 1H, $CHOCH_3$), 5.12 (m, 1H, CH-4), 6.66 (d, $J = 1.5$ Hz, 1H, CH-35), 7.44−7.93 (m, 21H, aromatic).

Per-(*R*)-2-NMA Esters of Squamocin. ^{1}H NMR (δ ppm, $CDCl_3$): 0.69 (t, $J = 7.1$ Hz, 3H, CH_3-34), 0.50−0.98 (m, 6H, CH_2-30, CH_2-31, and CH_2-32), 0.93 (m, 2H, CH_2-33), 1.03 (m, 2H, CH_2-29), 1.25 (m, 26H), 1.34 (m, 2H, CH_2-25), 1.40 (d, $J = 6.8$ Hz, 3H, CH_3-37), 1.08−1.62 (m, 8H, CH_2-17, CH_2-18, CH_2-21, and CH_2-22), 1.69 (ddd, $J = 13.6$, $J' = J'' = 4.0$ Hz, 2H, CH_2-14), 2.26 (dddd, $J = 9.2$, $J' = 3.4$, $J'' = J''' = 1.7$ Hz, 2H, CH_2-3), 3.21 (ddd, $J = J' = 7.5$, $J'' = 5.7$ Hz, 1H, CH-19 or CH-20), 3.37 (ddd, $J = J' = 7.5$, $J'' = 5.9$ Hz, 1H, CH-19 or CH-20), 3.41 (s, 3H, OCH_3), 3.44 (s, 3H, OCH_3), 3.46 (s, 3H, OCH_3), 3.74 (ddd, $J = J' = J'' = 7.1$ Hz, 1H, CH-23), 3.81 (ddd, $J = 7.2$, $J' = J'' = 4.2$ Hz, 1H, CH-16), 4.52 (m, 1H, CH-28), 4.81 (s, 1H, $CHOCH_3$), 4.84 (m, 1H, CH-24), 4.88 (s, 1H, $CHOCH_3$), 4.89 (m, 1H, CH-15), 4.94 (s, 1H, $CHOCH_3$), 4.99 (dq, $J = 1.7$, $J' = 6.8$ Hz, 1H, CH-36), 6.98 (q, $J = 1.6$ Hz, 1H, CH-35), 7.42−7.93 (m, 21H, aromatic).

Per-(*S*)-2-NMA Esters of Squamocin. ^{1}H NMR (δ ppm, $CDCl_3$): 0.72−1.27 (m, 26 H), 0.84 (t, $J = 6.8$ Hz, 3H, CH_3-34), 1.22 (m, 2H, CH_2-33), 1.31 (m, 4H, CH_2-14 and CH_2-25), 1.37 (m, 2H, CH_2-26), 1.40 (d, $J = 6.8$ Hz, 3H, CH_3-37), 1.44 (m, 4H, CH_2-27 and CH_2-29), 2.27 (dddd, $J = 8.6$, $J' = 3.4$, $J'' = J''' = 1.7$ Hz, 2H, CH_2-3), 2.86 (q, $J = 7.0$ Hz, 1H, CH-19 or CH-20), 3.410 (s, 3H, OCH_3), 3.413 (s, 3H, OCH_3), 3.45 (m, 1H, CH-19 or CH-20), 3.46 (s, 3H, OCH_3), 3.52 (m, 1H, CH-23), 3.67 (q, $J = 6.7$ Hz, 1H, CH-16), 4.75 (m, 1H, CH-24), 4.78 (m, 1H, CH-15), 4.82 (s, 1H, $CHOCH_3$), 4.84 (s, 1H, CH-28), 4.89 (s, 1H, $CHOCH_3$), 4.90 (s, 1H, $CHOCH_3$), 4.99 (dq, $J = 6.7$, $J' = 1.7$ Hz, 1H, CH-36), 6.98 (q, $J = 1.5$ Hz, 1H, CH-35), 7.40−7.93 (m, 21H, aromatic).

Per-(*R*)-2-NMA Esters of Rolliniastatin-2. ^{1}H NMR (δ ppm, $CDCl_3$): 0.77 (d, $J = 6.8$ Hz, 3H, CH_3-37), 0.81 (m, 2H, CH_2-26), 0.84 (m, 2H, CH_2-28), 0.96 (m, 2H, CH_2-29), 0.99 (m, 2H, CH_2-27), 1.07 (m, 2H, CH_2-30), 1.07−1.25 (m, 22H), 1.11−1.53 (m, 8H, CH_2-17, CH_2-18, CH_2-21, and CH_2-22), 1.37 (m, 2H, CH_2-25), 1.60 (m, 2H, CH_2-5), 1.64 (m, 2H, CH_2-14), 2.41 (ddd, $J = 5.9$, $J' = J'' = 1.4$ Hz, 2H, CH_2-3), 3.24 (ddd, $J = 7.8$, $J' = J'' = 5.6$ Hz, 1H, CH-19), 3.40 (ddd, $J = J' = J'' = 6.3$ Hz, 1H, CH-20), 3.453 (s, 3H, OCH_3), 3.455 (s, 3H, OCH_3), 3.463 (s, 3H, OCH_3), 3.77 (ddd, $J = J' = J'' = 6.5$ Hz, 1H, CH-23), 3.82 (ddd, $J = 7.0$, $J' = J'' = 3.8$ Hz, 1H, CH-16), 3.96 (dq, $J = 6.8$, $J' = 1.5$ Hz, 1H, CH-36), 4.88 (m, 2H, CH-15 and CH-24), 4.89 (s, 1H, $CHOCH_3$), 4.90 (s, 1H, $CHOCH_3$), 4.94 (s, 1H, $CHOCH_3$), 5.10 (dddd, $J = J' = J'' = J''' = 5.6$ Hz, 1H, CH-4), 5.82 (q, $J = 1.4$ Hz, 1H, CH-35), 7.45−7.93 (m, 21H, aromatic).

Per-(*S*)-2-NMA Esters of Rolliniastatin-2. ^{1}H NMR (δ ppm, $CDCl_3$): 0.70−1.25 (m, 32H), 0.88 (t, $J = 6.8$ Hz, 3H, CH_3-34), 1.11 (d, $J = 6.8$ Hz, 3H, CH_3-37), 1.27−1.58 (m, 8H, CH_2-17, CH_2-18, CH_2-21, and CH_2-22), 1.32 (m, 2H, CH_2-14), 1.46 (m, 2H, CH_2-5), 1.49 (m, 2H, CH_2-25), 2.53 (ddd, $J = 4.6$, $J' = J'' = 1.3$ Hz, 1H, CH-3a), 2.54 (ddd, $J = 6.9$, $J' = J'' = 1.4$ Hz, 1H, CH-3b), 3.03 (ddd, $J = J' = J'' = 4.3$ Hz, 1H, CH-19 or CH-20), 3.44 (s, 3H, OCH_3), 3.45 (s, 3H, OCH_3), 3.46 (s, 3H, OCH_3), 3.49 (m, 1H, CH-19 or CH-20), 3.72 (ddd, $J = J' = J'' = 6.8$ Hz, 1H, CH-16), 3.78 (ddd, $J = J' = J'' = 6.6$ Hz, 1H, CH-23), 4.63 (dq, $J = 6.8$, $J' = 1.6$ Hz, 1H, CH-36), 4.76 (ddd, $J = 8.8$, $J' = 5.7$, $J'' = 3.8$ Hz, 1H, CH-15), 4.906 (s, 1H, $CHOCH_3$), 4.910 (s, 2H, 2×($CHOCH_3$)), 5.02 (ddd, $J = 8.8$, $J' = J'' = 4.3$ Hz, 1H, CH-24), 5.13 (m, 1H, CH-4), 6.66 (q, $J = 1.5$ Hz, 1H, CH-35), 7.42−7.92 (m, 21H, aromatic).

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Supporting Information Available: Copies of NMR spectra of new compounds (5 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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