Towards the Total Synthesis of Pamamycin-607: Preparation of the Eastern Part (C^8–C^{18} Fragment)

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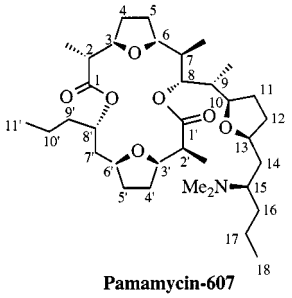
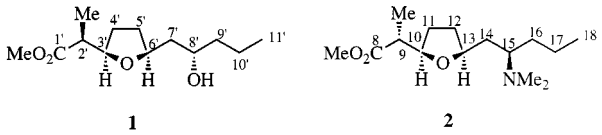
Pamamycin-607 belongs to a group of homologous macrodiolides, produced by various "*Streptomyces*", that possess remarkable autoregulatory antifungal, antibacterial and anion-transfering activities. The synthesis of the non-racemic C^8–C^{18} portion of pamamycin-607 is reported here and involves a route that features a stereoselective aldol condensation followed by a stereocontrolled reductive amination of the aldol and a *cis*-selective tetrahydrofuran formation by an intramolecular Michael cyclization induced by the geometry of the substrate.

Pamamycin-607 is the lowest member of a class of homologous macrodiolides expressed from various *Streptomyces spec.* such as *Streptomyces alboniger*[1] or *Streptomyces aurantiacus* JA 4570.[2] In 1987, Kondo et al.[3] reported the elucidation of the structure of this compound and its internal relative stereochemistry. Two years later its absolute configuration, represented in Scheme 1, has been established by chemical correlation with compounds of known absolute configurations.[4]



Pamamycin-607



1 **2**

Scheme 1

Pamamycin-607 possesses a remarkable range of chemical and biological activity. It induces aerial mycelium formation in an aerial mycelium-negative spontaneous mutant of the producing strain and it shows antimicrobial activity against phytopathogenic fungi and Gram positive bacteria. It also possesses the unique ability to transfer some anions (e.g. MnO_4^-) from the aqueous to the benzene layer at neutral and acidic pH values.[5] However, despite its unique structure and its various properties, the total synthesis of pamamycin-607 has not been reported in the literature so far, although several approaches to different fragments have been described.[6]

Recently, we started a project aimed at a convergent total synthesis of pamamycin-607 in which the fragments $C^{1'}-C^{11'}$ (**1**) and C^8-C^{18} (**2**) would be elaborated using a methodology developed in our laboratory for the synthesis of *cis*-2,5-disubstituted tetrahydrofurans.[7] We envisaged constructing the portion C^1-C^{18} by a *trans*-aldol reaction followed by formation of the third tetrahydrofuran ring using the Bartlett procedure.[8] We have already prepared the $C^{1'}-C^{11'}$ "*southern portion*" (**1**) of pamamycin-607[9] and in this paper we report an extension of our methodology to the synthesis of the C^8-C^{18} synthon **2**.

Examination of the structure of the two fragments **1** and **2** shows that the corresponding carbon atoms, $C^{3'}$ and C^{10} on the one hand and $C^{6'}$ and C^{13} on the other hand, have the same absolute configuration, indicating that the two fragments can be built starting from the same enantiomer **3**.[9] Two different routes were then considered for the synthesis of the disubstituted tetrahydrofuran **2**. In the first route the dimethylamino group would be introduced into the backbone in the last steps of the sequence by replacement of a hydroxy group with inversion of configuration (Mitsunobu or S_N2 reaction). One advantage of this strategy would be to have a common pathway to the late intermediate **4** for the synthesis of both fragments **1** and **2**. The Michael cyclization[9] of **4** will afford the two stereomers **5** and **6**, which could be converted into **1** and **2**, respectively (Scheme 2).

The second pathway, in which the amino group would be set up at an earlier stage of the synthesis, is shorter and seemed to pose more interesting synthetic problems, and so this route, depicted in Scheme 3, was selected and is detailed below.

Reductive amination of the 3-hydroxy ketone **7** with sodium cyanotrihydroborate in the presence of benzylamine

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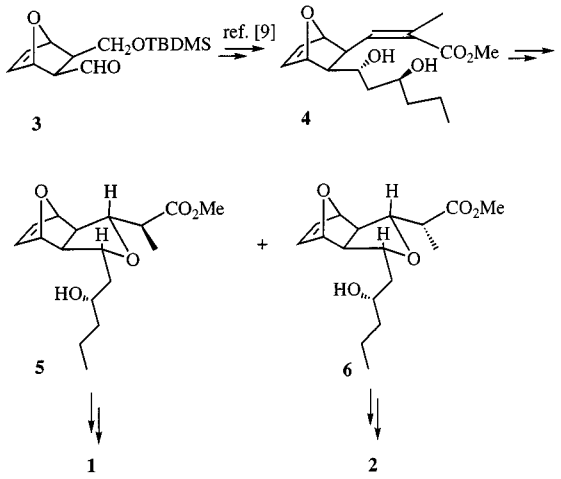
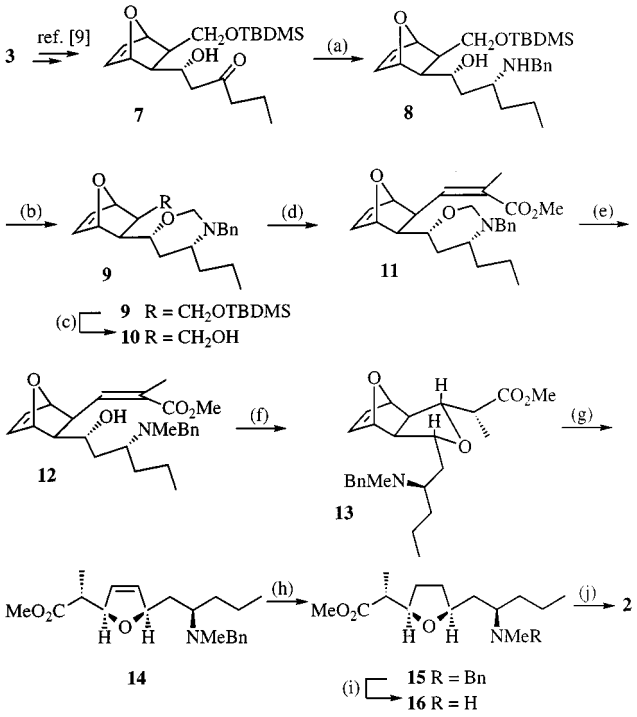


Scheme 2



Scheme 3. (a) $BnNH_2$, mol. sieves (4 Å), CH_3CO_2H then $NaBH_3CN$, −15°C, 70%; (b) HCHO aq., MeOH, room temp., 78%; (c) Bu_4NF, THF, 0°C, 86%; (d) i. Dess−Martin periodinane, C_5H_5N, CH_2Cl_2; ii. $(PhO)_2POCH(CH_3)CO_2Me$, NaH, THF, −78°C to 0°C, 56% overall; (e) $NaBH_3CN$, TFA, CH_3OH, 96%; (f) NaH, Et_2O, room temp., 90%; (g) 400°C, 10^{-3} Torr, 75%; (h) H_2, 5% Pt/C, CH_3CO_2Et, 41%; (i) H_2, 10% Pd/C, CH_3OH, 74%; (j) HCHO aq., CH_3CO_2H, $NaBH_3CN$, CH_3CN, 81%

and 4-Å molecular sieves, following the method described recently by Larchevêque,[10] afforded the *syn* diastereomer **8** (*syn*/*anti* = 90:10 determined by ^{1}H-NMR spectroscopy) in a highly stereoselective manner. The *syn* configuration of the OH and the NHBn groups in the major stereomer, which results from an external axial attack of the hydride,[10] has been confirmed by ^{13}C-NMR spectroscopy. In fact, in agreement with previous observations,[11] the chemical shifts of the carbons bound to the oxygen and the nitrogen atoms are higher for the major *syn* (δCHOH = 71.5, δCHNH = 57.4) than for the minor *anti* (δCHOH = 68.1, δCHNH = 55.0) stereomer.

The tetrahydrooxazine **9** was obtained in good yield upon treatment of **8** with aqueous formaldehyde in methanol.[12] Such protection of both the hydroxy and the amino groups seemed judicious to us since reductive deprotection should lead to a compound where one methyl group has already been installed on the nitrogen atom. The unsaturated ester **11** was then obtained under standard conditions: Regeneration of the primary alcohol by cleavage of the silyl ether **9** with tetrabutylammonium fluoride afforded **10**, which was oxidized with the Dess−Martin periodinane to give the corresponding, highly unstable, aldehyde. Without any purification the aldehyde was treated with the sodium salt of methyl 2-(diphenylphosphono)propionate[13] to give selectively the (*Z*)-α,β-unsaturated ester **11** [(*Z*)/(*E*) > 95:5]. We then planned to convert the cyclic aminal **11** to the γ-[benzyl(methyl)amino] alcohol **12** by reduction of the tetrahydro-1,3-oxazine ring. However, although the reduction by sodium tetrahydroborate of the homologous five-membered oxazolidine ring is quite easy and has been often reported,[14] six-membered tetrahydro-1,3-oxazines are not reduced by $NaBH_4$. The reductive cleavage of this ring required a more potent reducing agent, such as lithium aluminum hydride.[15] However, this reagent is not compatible with the ester group present in the molecule. We tried to facilitate the reduction by prior formation of an iminium salt and we were gratified with the excellent yield of the reduction **11** → **12** (96%) obtained by treatment of **11** with an excess of sodium cyanotrihydroborate followed by one equivalent of trifluoroacetic acid at room temperature. Treatment of **12** with NaH in THF gave rise to an intramolecular Michael cyclization leading to the tricyclic compound **13** as the major stereomer (**13**/C^9 stereomer = 60:40). As anticipated,[7] if only the *cis*-disubstituted tetrahydrofurans were obtained, the configuration of the carbon atom bearing the methyl and the methoxycarbonyl groups could not be well controlled. The ratio of the two diastereomers formed is representative of a thermodynamic equilibrium but, due to the difficulty of separation at this stage, the yield of **13** could not be improved by purification and equilibration of the minor isomer. A Diels−Alder reaction under flash thermolysis conditions (400°C, 10^{-3} Torr), followed by catalytic hydrogenation (5% Pt/C), gave the desired, yet highly unstable, tetrahydrofuran **15**, which was separated easily from its diastereomer by column chromatography on silica gel. After debenzylation, the second methyl group was introduced on the nitrogen atom by a standard method.[16] The *anti* configuration of the methyl group in **2** was confirmed by ^{1}H-NMR spectroscopy, considering the chemical shift of its signal (δ = 1.12) compared to that of the other diastereomer (δ = 1.24). Both of these values are in good agreement with literature values.[8]

In conclusion, we have described here the first synthesis of the fragment C^8−C^{18} of pamamycin-607 in 11 steps starting for aldehyde **3**. The synthesis of the third portion of this molecule, as well as the couplings of the three fragments, is currently underway in our laboratory

Experimental Section

For general experimental information, see ref.[9]

(1*S*,2*S*,3*R*,4*R*,1′*R*,3′*R*)-2-(3′-*N*-Benzylaminohexyl-1′-hydroxy)-3-*tert*-butyldimethylsilyloxymethyl-7-oxabicyclo[2.2.1]hept-5-ene (8): To a mixture of cetol **7** (2.65 g, 7.47 mmol), benzylamine (3.20 g, 29.9 mmol) and 4-Å molecular sieves (4 g) in THF (90 mL) at 0°C was added acetic acid (3.59 g, 59.8 mmol). The mixture was stirred for 15 min then cooled to −15°C. $NaBH_3CN$ (0.94 g, 14.95 mmol) was added in two portions and the mixture was stirred for 36 h at −15°C. The mixture was hydrolysed with 1 M NaOH (70 mL) and extracted with ether (3 × 100 mL). The combined organic layers were washed with brine (50 mL), dried with $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (ethyl acetate/petroleum ether, 1:1, containing 5% methanol) to give 2.3 g (70%) of amino alcohol **8** as a colorless oil. − $[\alpha]_D^{20}$ = −54 (*c* = 1.0, $CHCl_3$). − IR (film): $\tilde{\nu}$ = 3300 cm^{-1} (br. s, OH), 2965 (vs, C−H), 2940 (vs, C−H), 2860 (vs, C−H), 1470 (m, C=C). − ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 0.10 (s, 6 H), 0.93 (s, 9 H), 0.97 (t, *J* = 6.9 Hz, 3 H), 1.2−1.5 (m, 5 H), 1.6 (m, 3 H), 1.78−1.92 (m, 2 H), 2.82 (m, 1 H), 3.61 (t, *J* = 10.1 Hz, 1 H), 3.72 (t, *J* = 9.0 Hz, 1 H), 3.73 (d, *J* = 12.5 Hz, 1 H), 3.93 (d, *J* = 12.5 Hz, 1 H), 4.29 (dd, *J* = 9.9, 5.3 Hz, 1 H), 4.72 (s, 1 H), 4.94 (s, 1 H), 6.36 (m, 2 H), 7.32 (m, 5 H). − ^{13}C NMR ($CDCl_3$, 63 MHz): δ = −5.5 (SiCH_3), −5.4 (SiCH_3), 14.0 (C-6′), 18.1 (Si*C*), 18.6 (C-5′), 25.8 (*t*Bu), 36.2 (C-4′), 38.7 (C-2′), 42.5 (C-3), 47.9 (C-2), 49.9 (CH_2Ph), 57.4 (C-3′), 63.0 (CH_2O), 71.5 (C-1′), 79.6 (C-1), 80.3 (C-4), 127.0, 128.1, 128.2, 135.0 (C-6), 136.0 (C-5), 139.1. − CIMS; *m*/*z* (%): 446 (MH^+, 100), 445 (M^+, 24), 162 (5). − $C_{26}H_{43}NO_3Si$ (445): calcd. C 70.06, H 9.72, N 3.14; found C 69.79, H 9.57, N 3.46.

(1*S*,2*S*,3*R*,4*R*,1′*R*,3′*R*)-2-(4′-Benzyl-3′-propyl-4′,6′-tetrahydrooxazinyl)-3-*tert*-butyldimethylsilyloxymethyl-7-oxabicyclo[2.2.1]hept-5-ene (9): To a solution of amino alcohol **8** (1.86 g, 4.17 mmol) in methanol (50 mL) was added a 30% aqueous solution of formaldehyde (580 μL, 20.8 mmol) at room temperature. After 1 h, the solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel (ether/petroleum ether, 80:20, 1% NH_4OH) to give 1.48 g (78%) of tetrahydrooxazine **9** as a colorless oil. − $[\alpha]_D^{20}$ = +14 (*c* = 1.0, $CHCl_3$). − IR (film): $\tilde{\nu}$ = 3020 cm^{-1} (w, C=C), 2965 (vs, C−H), 2940 (vs, C−H), 1500 (w, C=C). − ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 0.04 (s, 3 H), 0.05 (s, 3 H), 0.90 (s, 9 H), 0.95 (t, *J* = 7.0 Hz, 3 H), 1.37−1.91 (m, 8 H), 3.05 (m, 1 H), 3.42 (dt, *J* = 2.1, 10.2 Hz, 1 H), 3.52 (t, *J* = 10.2 Hz, 1 H), 3.61 (t, *J* = 13.6 Hz, 1 H), 3.86 (d, *J* = 13.6 Hz, 1 H), 4.10 (d, *J* = 10.4 Hz, 1 H), 4.16 (dd, *J* = 4.3, 9.6 Hz, 1 H), 4.34 (d, *J* = 10.4 Hz, 1 H), 4.81 (s, 1 H), 5.00 (s, 1 H), 6.38 (m, 2 H), 7.25−7.40 (m, 5 H). − ^{13}C NMR ($CDCl_3$, 63 MHz): δ = −5.4 (SiCH_3), −5.3 (SiCH_3), 14.1 (C-3″), 18.2 (Si*C*), 18.9 (C-2″), 25.9 (*t*Bu), 32.3 (C-1″), 36.1 (C-2′), 42.5 (C-3), 45.8 (C-2), 47.0 (CH_2Ph), 58.9 (C-3′), 62.5 (CH_2O), 76.5 (C-1′), 78.59, 80.3 (C-4), 82.5 (C-5′), 126.7, 128.1, 128.7, 135.7 (C-5,6), 139.4. − CIMS; *m*/*z* (%): 458 (MH^+, 100), 415 (8), 414 (18), 346 (9). − $C_{27}H_{43}NO_3Si$ (457): calcd. C 70.85, H 9.47; found C 70.24, H 9.31.

(1*S*,2*S*,3*R*,4*R*,1′*R*,3′*R*)-2-(4′-Benzyl-3′-propyl-4′,6′-tetrahydrooxazinyl)-3-hydroxymethyl-7-oxabicyclo[2.2.1]hept-5-ene (10): To a solution of silyl ether **9** (1.48 g, 3.23 mmol) in THF (15 mL), cooled at 0°C, was added dropwise a 1 M solution of tetrabutylammonium fluoride in THF (4.5 mL, 4.5 mmol). The solution was stirred for 2 h, allowed to warm up to room temperature, and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (ether acetate/petroleum ether, 1:1) to give 960 mg (86%) of alcohol **10** as a white solid. − M.p. 132°C. − $[\alpha]_D^{20}$ = +63 (*c* = 1.01, $CHCl_3$). − IR (KBr): $\tilde{\nu}$ = 3450 cm^{-1} (br. s, OH), 3020 (w, C=C), 1500 (w, C=C). − ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 0.97 (t, *J* = 7.0 Hz, 3 H), 1.42−1.77 (m, 6 H), 1.86 (dd, *J* = 7.8, 10.2 Hz, 1 H), 2.01 (m, 1 H), 3.15 (m, 1 H), 3.62−3.96 (m, 6 H), 4.24 (d, *J* = 10.7 Hz, 1 H), 4.38 (d, *J* = 10.3 Hz, 1 H), 4.68 (s, 1 H), 4.84 (s, 1 H), 6.36 (m, 1 H), 6.47 (m, 1 H), 7.24−7.33 (m, 5 H). − ^{13}C NMR ($CDCl_3$, 63 MHz): δ = 13.9, 18.7, 31.9, 35.7, 43.4, 46.0, 46.5, 58.4, 62.7, 76.5, 78.8, 81.5, 82.3, 126.7, 128.0, 128.6, 135.2, 136.1, 138.6. − CIMS; *m*/*z* (%): 344 (MH^+, 100), 343 (M^+, 9), 300 (14). − $C_{21}H_{29}O_3N$ (343): calcd. C 73.44, H 8.51; found C 73.18, H 8.42.

(1*S*,2*S*,3*S*,4*S*,1′*R*,3′*R*)-2-(4′-Benzyl-3′-propyl-4′,6′-tetrahydrooxazinyl)-3-(2″-methoxycarbonylprop-1″-enyl)-7-oxabicyclo[2.2.1]-hept-5-ene (11): To a solution of alcohol **10** (960 mg, 2.79 mmol) in anhydrous dichloromethane (40 mL) and pyridine (442 mg, 5.58 mmol) cooled at 0°C was added Dess−Martin periodinane (1.37 g, 3.21 mmol). The mixture was stirred for 30 min, diluted with ether (100 mL), washed successively with water, saturated aqueous solutions of $NaHCO_3$, then $Na_2S_2O_3$ and water. The combined aqueous layers were extracted with ether (2 × 20 mL). The combined organic layers were dried with $MgSO_4$ and concentrated under reduced pressure to give the crude aldehyde, which was used without purification. − To a suspension of NaH (80 mg, 3.34 mmol) in anhydrous THF (1 mL), cooled at −78°C, was added dropwise a solution of methyl 2-(diphenylphosphono)propionate (987 mg, 3.13 mmol). The mixture was stirred for 30 min and a solution of the crude aldehyde in THF (3 mL) was added. The reaction mixture was stirred at −78°C for 1 h then allowed to warm slowly to 0°C over 3 h. The reaction mixture was quenched with saturated aqueous ammonium chloride (15 mL). The aqueous layers were extracted with ether (3 × 20 mL). The combined organic layers were dried with $MgSO_4$ and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (ether/petroleum ether, 1:1) to give 650 mg (56%) of (*Z*) olefin **11** as a colorless oil. − $[\alpha]_D^{20}$ = +116 (*c* = 1.02, $CHCl_3$). − IR (film): $\tilde{\nu}$ = 2960 cm^{-1} (vs, C−H), 1740 (s, C=O), 1650 (m, C=C), 1500 (m, C=C). − ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 0.94 (t, *J* = 6.9 Hz, 3 H), 1.38−1.66 (m, 6 H), 1.93 (s, 3 H), 1.97 (dd, *J* = 7.2, 8.2 Hz, 1 H), 2.97 (m, 1 H), 3.39 (dd, *J* = 9.5, 8.8 Hz, 1 H), 3.52 (m, 1 H), 3.61 (d, *J* = 13.5 Hz, 1 H), 3.69 (s, 3 H), 3.86 (d, *J* = 13.5 Hz, 1 H), 4.08 (d, *J* = 10.4 Hz, 1 H), 4.30 (d, *J* = 10.4 Hz, 1 H), 4.66 (s, 1 H), 4.96 (s, 1 H), 6.07 (dd, *J* = 10.1, 1.3 Hz, 1 H), 6.40 (dd, *J* = 5.8, 1.5 Hz, 1 H), 6.45 (dd, *J* = 5.8, 1.5 Hz, 1 H), 7.2−7.38 (m, 5 H). − ^{13}C NMR ($CDCl_3$, 63 MHz): δ = 13.9 (C-3‴), 18.9 (C-2‴), 20.5 (C-3″), 31.0 (C-1‴), 36.0 (C-2″), 39.7 (C-3), 47.0 (CH_2Ph), 47.8 (C-2), 51.1 (OCH_3), 59.1 (C-3′), 77.0 (C-1′), 78.9 (C-1), 82.8 (C-5′), 83.9 (C-4), 126.6, 127.3 (C-2″), 128.0, 128.7, 135.0 (C-6), 136.5 (C-5), 139.3, 144.1 (C-1″), 167.9 (C=O). − CIMS; *m*/*z* (%): 412 (MH^+, 100), 411 (M^+, 9), 368 (10). − $C_{25}H_{33}NO_4$ (411): calcd. C 72.96, H 8.08; found C 72.79, H 8.22.

(1*S*,2*S*,3*S*,4*S*,1′*R*,3′*R*)-2-[1′-Hydroxy-3′-(*N*,*N*-methylbenzylamino)hexyl]-3-(2″-methoxycarbonylprop-1″-enyl)-7-oxabicyclo-[2.2.1]hept-5-ene (12): To a solution of tetrahydrooxazine **11** (650 mg, 1.58 mmol) and sodium cyanotrihydroborate (250 mg, 3.98 mmol) in anhydrous methanol (15 mL) was slowly added dropwise anhydrous trifluoroacetic acid (120 μL, 1.58 mmol). The reaction mixture was stirred at room temperature for 30 min, quenched with aqueous saturated sodium bicarbonate (10 mL), concentrated in vacuo, diluted with water (40 mL) and extracted with dichloromethane (4 × 40 mL). The combined organic layers were dried with $MgSO_4$. Evaporation of the solvent under reduced pressure yielded pure amino alcohol **12** (625 mg, 96%) as a colorless oil. − $[\alpha]_D^{20}$ = +74 (*c* = 1.0, $CHCl_3$). − IR (film): $\tilde{\nu}$ = 3200 cm^{-1} (br. s, OH), 3030 (w, C=C), 1710 (s, C=O), 1650 (m,

C=C). − ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 0.94 (t, *J* = 6.9 Hz, 3 H), 1.10−1.62 (m, 7 H), 1.92 (s, 3 H), 2.00 (dd, *J* = 5.0, 8.4 Hz, 1 H), 2.15 (s, 3 H), 2.68 (m, 1 H), 3.28 (t, *J* = 9.2 Hz, 1 H), 3.53 (d, *J* = 12.8 Hz, 1 H), 3.72 (d, *J* = 12.8 Hz, 1 H), 3.74 (m, 4 H), 4.63 (s, 1 H), 4.97 (s, 1 H), 6.12 (dd, *J* = 10.6, 5.8 Hz, 1 H), 6.35 (dd, *J* = 1.6, 5.8 Hz, 1 H), 6.44 (dd, *J* = 1.7, 5.8 Hz, 1 H), 7.23−7.32 (m, 5 H). − ^{13}C NMR ($CDCl_3$, 63 MHz): δ = 14.1, 20.5, 20.6, 28.6, 32.6, 35.0, 40.2, 48.7, 51.2, 58.4, 63.9, 73.0, 79.1, 83.7, 127.1, 127.2, 128.3, 128.9, 134.7, 136.9, 138.0, 145.0, 167.8. − CIMS; *m*/*z* (%): 414 (MH^+, 100), 413 (M^+, 5), 346 (7), 314 (8), 282 (5), 176 (7). − $C_{25}H_{35}NO_4$ (413): calcd. C 72.61, H 8.53; found C 72.39, H 8.55.

(1*S*,2*S*,3*R*,5*R*,6*S*,7*R*,2′*R*,1″*R*)-5-(1″-Methoxycarbonylethyl)-3-[2′-(*N*,*N*-methylbenzylamino)pentyl]-4,10-dioxatricyclo[5.2.1.0^{2,6}]dec-8-ene (13): To a solution of amino alcohol **12** (252 mg, 1.64 mmol) in anhydrous ether was added a 50% suspension of NaH in oil (8 mg, 0.165 mmol). The mixture was stirred for 2.5 h, quenched with saturated aqueous ammonium chloride (0.5 mL), dried with $MgSO_4$, and concentrated in vacuo. The residue was purified by chromatography on silica gel (CH_2Cl_2/methanol, 95:5) to give 229 mg (90%) of a mixture of the two diastereomers **13** and **13′** [(*S*) configuration for C-1″] in the proportion 60:40. Flash chromatography led to a sample of **13** (90% purity) that gave the following spectral data: ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 0.93 (t, *J* = 7.0 Hz, 3 H), 1.21 (d, *J* = 7.0 Hz, 3 H), 1.25−1.65 (m, 5 H), 1.96 (m, 1 H), 2.09 (m, 1 H), 2.15 (s, 3 H), 2.24 (m, 1 H), 2.64−2.77 (m, 2 H), 3.52 (d, *J* = 13.6 Hz, 1 H), 3.60 (d, *J* = 13.6 Hz, 1 H), 3.69 (s, 3 H), 3.82 (t, *J* = 7.1 Hz, 2 H), 4.63 (d, *J* = 0.8 Hz, 1 H), 4.68 (d, *J* = 1.0 Hz, 1 H), 6.32 (dd, *J* = 5.8, 1.4 Hz, 1H), 6.37 (dd, *J* = 5.8, 1.5 Hz, 1 H), 7.18−7.26 (m, 5 H). − ^{13}C NMR ($CDCl_3$, 63 MHz): δ = 12.6 (C-5′), 14.2 (C-2″), 20.3 (C-4′), 31.3 (C-3′), 35.5 (C-2′), 36.4 (N*C*H$_3$), 43.7 (C-1″), 51.6 (O*C*H$_3$), 51.8 (C-6), 54.6 (C-2), 57.3 (C-2′), 59.7 (N*C*H$_2$Ph), 79.2 (C-3), 80.2 (C-1), 80.8 (C-5), 81.6 (C-7), 126.7, 128.2, 128.7, 136.4 (C-8), 136.5 (C-9), 140.2, 175.0 (C=O). − HRMS: calcd. for $C_{25}H_{36}NO_4$: 414.2644, found [MH^+] 414.2644.

Methyl (2*R*,3*R*,6*S*,8*R*)-2-Methyl-8-(*N*,*N*-methylbenzylamino)-3,6-epoxy-4-undecenoate (14): The mixture of diastereomers **13** and **13′** (228 mg, 0.551 mmol) was evaporated through a hot horizontal mullite tube (400°C, 10^{-3} Torr) and the thermolysate was collected on a cold finger cooled to liquid nitrogen temperature. After warming the apparatus to room temperature, the finger was washed with ether and the resulting solution was dried with $MgSO_4$ and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (ethyl acetate/petroleum ether, 1:1) to give 142 mg (75%) of a mixture of the diastereomers **14** and **14′** (epimer at C-2). A sample enriched by chromatography (**14**/**14′** = 85:15) gave the following spectral data for **14**: IR (film): $\tilde{\nu}$ = 3030 cm^{-1} (w, C=C), 2940 (vs, C−H), 1735 (s, C=O), 1505 (w, C=C). − ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 0.92 (t, *J* = 7.0 Hz, 3 H), 1.15 (d, *J* = 7.1 Hz, 3 H), 1.25−1.55 (m, 5 H), 1.87 (dt, *J* = 13.5, 6.9 Hz, 1 H), 2.13 (s, 3 H), 2.61 (dq, *J* = 6.8, 7.1 Hz, 1 H), 2.72 (d, *J* = 6.7 Hz, 1 H), 3.55 (s, 2 H), 3.69 (s, 3 H), 4.98 (m, 2 H), 5.83 (dd, *J* = 11.0, 6.5 Hz, 1 H), 7.22−7.33 (m, 5 H). − ^{13}C NMR ($CDCl_3$, 63 MHz): δ = 12.7 (C-11), 14.2 (C-12), 20.2 (C-10), 32.0 (C-9), 36.0 (C-7), 37.1 (N*C*H$_3$), 46.1 (C-2), 51.6 (O*C*H$_3$), 57.8 (C-8), 59.2 (N*C*H$_2$Ph), 84.2 (C-6), 86.7 (C-3), 126.6, 128.0, 128.6, 132.2 (C-4, C-5), 140.4, 174.8 (C-1). − HRMS: calcd. for $C_{21}H_{32}NO_3$: 346.2382,found [MH^+] 346.2386.

Methyl (2*R*,3*R*,6*S*,8*R*)-2-Methyl-8-(*N*,*N*-methylbenzylamino)-3,6-epoxyundecenoate (15) and Its (2*S*,3*R*,6*S*,8*R*) Stereomer 15′: A mixture of diastereomers **14** and **14′** (140 mg, 0.405 mmol) was dissolved in ethyl acetate (10 mL) and hydrogenated in the presence of 5% Pt/C (15 mg) at atmospheric pressure for 1 h. After filtration, the catalyst was washed with ethyl acetate and the filtrates were concentrated in vacuo. The oily residue was purified by chromatography on silica gel (ethyl acetate/petroleum ether, 2:3, containing methanol 5%) to give 48 mg (34%) of diastereomers **15′** and 57 mg (41%) of diastereomer **15** as colorless oils. Spectral data for **15′** and **15** are as follows: **15′** (2*S*,3*R*,6*S*,8*R*): $[\alpha]_D^{20}$ = +1.7 (*c* = 1.06, $CHCl_3$). − IR (film): $\tilde{\nu}$ = 3030 cm^{-1} (w, C=C), 2955 (vs, C−H), 1740 (s, C=O), 1500 (m, C=C). − ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 0.92 (t, *J* = 7.0 Hz, 3 H), 1.24 (d, *J* = 7.0 Hz, 3 H), 1.25−1.70 (m, 7 H), 1.93 (m, 3 H), 2.13 (s, 3 H), 2.53 (dq, *J* = 7.2, 7.1 Hz, 1 H), 2.62 (t, *J* = 6.8 Hz, 1 H), 3.55 (d, *J* = 1.2 Hz, 2 H), 3.69 (s, 2 H), 4.00 (m, 2 H), 7.22−7.33 (m, 5 H). − ^{13}C NMR ($CDCl_3$, 63 MHz): δ = 14.1 (C-11), 14.2 (C-12), 20.2 (C-10), 29.2 (C-5), 31.0 (C-9), 31.8 (C-4), 36.1 (C-7), 36.3 (N*C*H$_3$), 45.3 (C-2), 51.5 (O*C*H$_3$), 57.9 (C-8), 59.6, (N*C*H$_2$Ph), 77.7 (C-6), 79.8 (C-3), 126.6, 128.0, 128.6, 140.5, 175.1 (C-1). − HRMS: calcd. for $C_{21}H_{34}NO_3$: 348.2539, found [MH^+] 348.2539. − **15** (2*R*,3*R*,6*S*,8*R*): $[\alpha]^{20}_D$ = −24.8 (*c* = 1.2, $CHCl_3$). − IR (film): $\tilde{\nu}$ = 3030 cm^{-1} (w, C=C), 2935 (vs, C−H), 1740 (s, C=O), 1495 (m, C=C). − ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 0.92 (t, *J* = 7.0 Hz, 3 H), 1.13 (d, *J* = 7.0 Hz, 3 H), 1.24−1.68 (m, 7 H), 1.84−1.98 (m, 3 H), 2.12 (s, 3 H), 2.55 (dq, *J* = 7.9, 7.0 Hz, 1 H), 2.63 (t, *J* = 6.8 Hz, 1 H), 3.54 (s, 2 H), 3.69 (s, 3 H), 4.03 (m, 2 H), 7.22−7.33 (m, 5 H). − ^{13}C NMR ($CDCl_3$, 63 MHz): δ = 13.3 (C-11), 14.3 (C-12), 20.2 (C-10), 28.5 (C-5), 30.9 (C-9), 31.9 (C-4), 36.1 (C-7), 36.2 (N*C*H$_3$), 45.5 (C-2), 51.6 (O*C*H$_3$), 57.9 (C-8), 59.7 (N*C*H$_2$Ph), 77.7 (C-6), 80.1 (C-3), 126.6, 128.0, 128.6, 140.6, 175.4 (C-1). − HRMS: calcd. for $C_{21}H_{34}NO_3$: 348.2539, found [MH^+] 348.2540.

Methyl (2*R*,3*R*,6*S*,8*R*)-2-Methyl-8-methylamino-3,6-epoxyundecanoate (16): A solution of benzylamino compound **15** (55 mg, 0.158 mmol) in methanol (3 mL) was hydrogenated in the presence of 10% Pd/C (15 mg) at atmospheric pressure for 45 min. After filtration, the catalyst was washed with methanol and the filtrate was concentrated in vacuo. The residue was purified by chromatography on silica gel (ethyl acetate/methanol, 1:1, containing 2‰ NH_4OH) to give 30 mg (74%) of methylamino compound **16** as a colorless oil. − $[\alpha]_D^{20}$ = −28.2 (*c* = 0.85, $CHCl_3$). − IR (film): $\tilde{\nu}$ = 3360 cm^{-1} (m, NH), 2955 (vs, C−H), 1740 (s, C=O), 1460 (m, C=C). − ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 0.90 (t, *J* = 6.9 Hz, 3 H), 1.08 (d, *J* = 7.0 Hz, 3 H), 1.20−1.60 (m, 8 H), 1.84−2.10 (m, 3 H), 2.33 (s, 3 H), 2.47 (m, 2 H), 3.66 (s, 3 H), 3.95 (m, 2 H). − ^{13}C NMR ($CDCl_3$, 63 MHz): δ = 13.3, 14.3, 18.7, 28.3, 31.8, 33.4, 36.0, 40.0, 45.4, 51.5, 58.4, 78.8, 80.8, 175.4. − HRMS: calcd. for $C_{14}H_{28}NO_3$: 258.2069, found [MH^+] 258.2067.

Methyl (2*R*,3*R*,6*S*,8*R*)-8-Dimethylamino-2-methyl-3,6-epoxyundecanoate (2): To a solution of methylamino compound **16** (29 mg, 0.113 mmol) in a mixture of acetonitrile (4 mL), 20% aqueous formaldehyde (170 μL), and acetic acid (6.5 μL, 0.113 mmol), was added sodium cyanotrihydroborate (14.2 mg, 0.225 mmol). The mixture was stirred at room temperature for 2 h, quenched with saturated aqueous sodium bicarbonate (5 mL) and extracted with dichloromethane (3 × 10 mL). The combined organic layers were dried with $MgSO_4$ and concentrated in vacuo. The residue was purified by chromatography on silica gel (ethyl acetate/methanol, 3:2, containing 2‰ NH_4OH) to give 25 mg (81%) of dimethylamino compound **2** as a colorless oil. − $[\alpha]_D^{20}$ = −23.9 (*c* = 0.715, $CHCl_3$). − IR (film): $\tilde{\nu}$ = 2960 cm^{-1} (vs, C−H), 2820 (m, C−H), 2775 (m, C−H), 1740 (s, C=O). − ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 0.90 (t, *J* = 6.9 Hz, 3 H), 1.12 (d, *J* = 7.0 Hz, 3 H), 1.18−1.51 (m, 6 H), 1.60 (m, 1 H), 1.79 (dq, *J* = 13.6, 6.8 Hz, 1 H), 1.99 (m, 2 H), 2.21 (s, 6 H), 2.48 (m, 2 H), 3.69 (s, 3 H), 3.94 (t, *J* = 6.8 Hz,

1 H), 4.03 (dd, J = 6.8, 8.0 Hz, 1 H). – ^{13}C NMR ($CDCl_3$, 63 MHz): δ = 13.3 (C-11), 14.2 (C-12), 20.2 (C-10), 28.5 (C-5), 31.1 (C-9), 31.7 (C-4), 35.5 (C-7), 40.1 [$N(CH_3)_2$], 45.5 (C-2), 51.5 (OCH_3), 60.6 (C-8), 77.6 (C-6), 80.1 (C-3), 175.4 (C-1). – HRMS: calcd. for $C_{15}H_{30}NO_3$: 272.2226, found [MH^+] 272.2229.

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