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A novel and efficient stereoselective synthesis of the southern part of pamamycin-607

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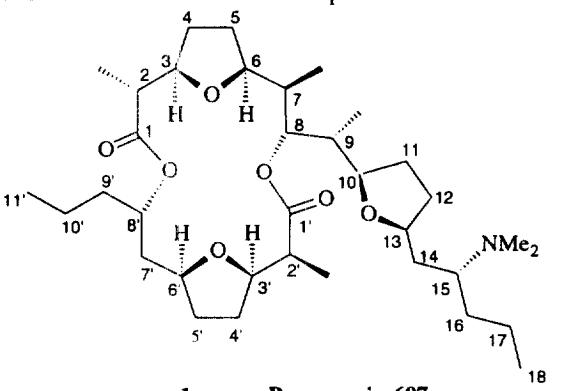
Abstract: The C_1'C_{11}' portion of the antibiotic pamamycin-607 was synthesized from the enantiomerically pure hydroxy acetate **3**, readily available by enzymatic transesterification of the corresponding diol with vinylacetate. This synthesis entailed a series of stereoselective transformations: the absolute configurations of $C_{6'}$ and $C_{8'}$ were fixed by an aldol condensation followed by an anti-reduction of the resulting β-hydroxyketone. The configurations of the last two asymmetric centers $C_{2'}$ and $C_{3'}$ were controlled by a novel highly diastereoselective intramolecular cyclization catalyzed by fluoride ions. © 1997 Elsevier Science Ltd

The pamamycins are a class of homologous macrodiolides which have been isolated from *Streptomyces alboniger* in 1979.[1] A few years later, Marumo *et al.*[2] isolated and purified a pamamycin possessing a molecular weight of 607 which was named pamamycin-607. Its structure and internal relative stereochemistry was established on the basis of spectral analysis by 2D ^1H–^{13}C and ^1H–^1H correlations via NMR and NOE difference spectroscopy.[2] Its absolute configuration represented by **1** has been determined by chemical correlation with compounds of known absolute configuration.[3]



1 **Pamamycin-607**

Four new pamamycin homologues with molecular weights of 635 and 649 have since been purified and their structures elucidated by spectral analysis and chemical degradation.[4]

Pamamycin-607 shows remarkable biological activities: it induces aerial mycelium formation in an aerial mycelium-negative mutant of *Streptomyces alboniger* and it exhibits antibiotic activity against Gram positive bacteria and pathogenic fungi.[5] Furthermore it possesses the ability to transfer lipophilic anions from acidic and neutral aqueous solutions to organic phases. In view of the unique structure of pamamycin-607 and its various biological properties, the development of a synthetic route to this natural product would be useful. Two groups are, for the moment, involved in the total synthesis of **1**: the group of Walkup *et al.* has already reported the synthesis of the C_1'C_{11}' portion **2** in racemic[6] and in optically active form[7] as well as the synthesis of the C_1C_{14} subunit of this pamamycin;[8] the

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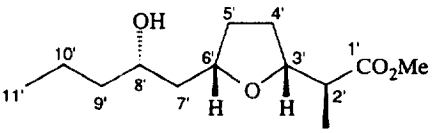
group of Perlmutter *et al.* has recently published the synthesis of the enantiomerically enriched 8′-epi $C_{1'}C_{11'}$ fragment.[9]

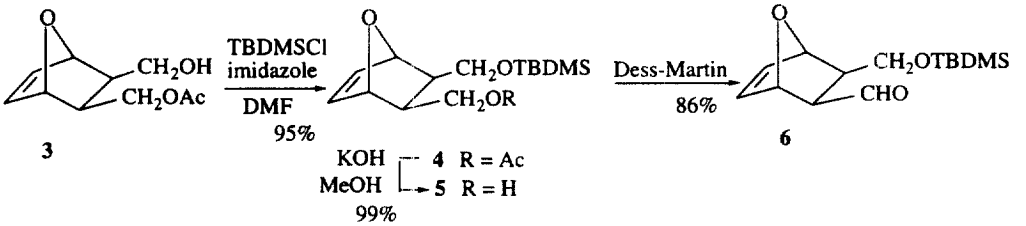


2

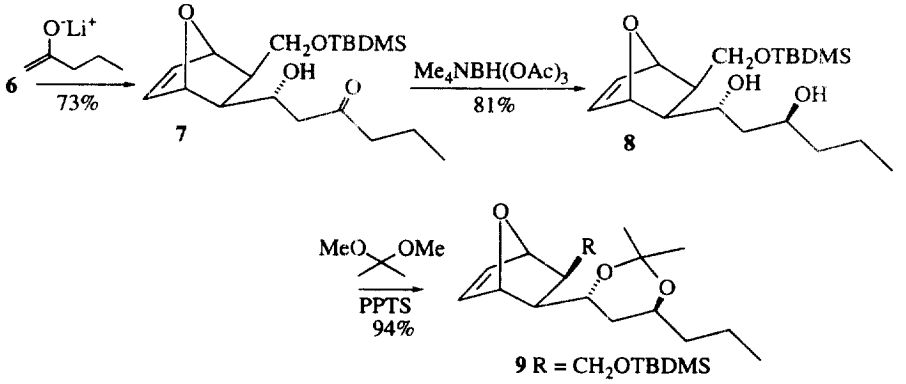
We have recently found a new method for the highly stereoselective synthesis of either *cis*- or *trans*-2,5-disubstituted tetrahydrofurans via an intramolecular Michael reaction[10] and this methodology has been applied to the synthesis of (+)-methyl nonactate.[11] We decided to demonstrate the versatility of our method by the total synthesis of pamamycin-607 since three *cis*-2,5-disubstituted tetrahydrofuran rings are present in its structure. This article describes the synthesis of the southern $C_{1'}C_{11'}$ portion **2** of this antibiotic.

The key step of this synthesis involves a highly stereoselective Michael cyclization induced by the fluoride ion F^- which leads also to a new and unexpectedly excellent control of the configuration of the $C_{2'}$ asymmetric center.

The synthesis started from the aldehyde **6** obtained by classical reactions from the enantiomerically pure hydroxy acetate **3** easily prepared via an enzymatic transesterification.[12]



The aldehyde **6** reacted with the kinetic lithium enolate of 2-pentanone to give the aldol **7** as the major product (de=80%). The configuration of the newly created asymmetric center was assigned by careful examination of the ^1H NMR spectrum of the lactone[13] obtained after oxidation of the diol arising from the deprotection of the silyl ether function of the aldol **7**. Under the conditions described by Evans *et al.*[14] the aldol product **7** was selectively reduced by tetramethylammonium triacetoxy borohydride to give the *anti* diastereomer **8** (*anti*/*syn*=80/20). The *anti* configuration was confirmed by ^{13}C NMR spectroscopy after conversion of **8** to the corresponding acetonide **9**: the values of the ^{13}C chemical shifts of the acetal methyl groups (δ=24.4 and 24.8 ppm) and of the acetal carbon (=100.1 ppm) are in excellent agreement with the values reported in the literature for *anti*-1,3-diol acetonides.[15]



The desired α,β-unsaturated ester **13** was then obtained under standard conditions: regeneration of the primary alcohol by treatment of **9** with tetrabutylammonium fluoride gave **10** which was oxidized

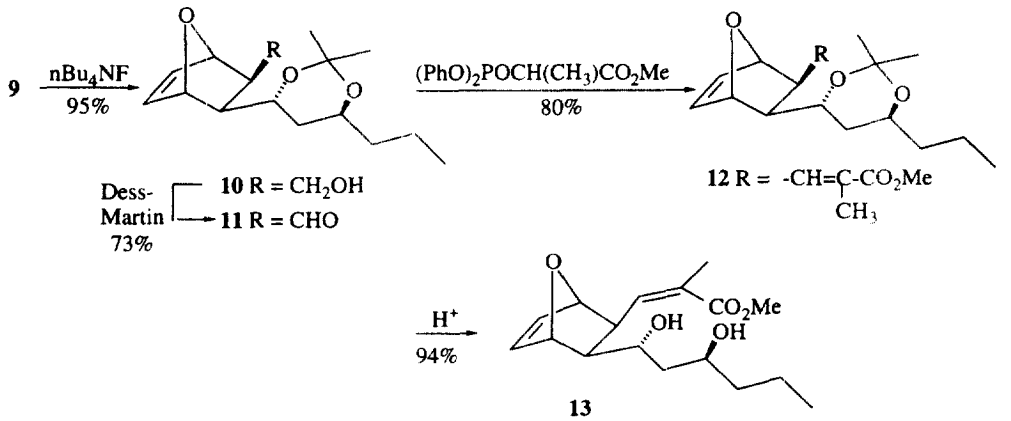
Table 1. Selectivity of the Michael cyclization of **14**

Entry	*Base*	*Conditions*	*ratio* [a]
1	$BnMe_3NOMe$	MeOH, 20°C, 6 h	50 / 50
2	MeONa	MeOH, 20°C, 6 h	50 / 50
3	P_4-t-Bu [b]	THF, 20°C, 5 mn	60 / 40
4	nBu_4NF	THF, 20°C, 1 h	80 / 20
5	KF, 18C6	CH_3CN, reflux, 6 h	80 / 20

[a] The ratios **15/15'** have been determined by integration, on the ^1H NMR spectra of the crude mixture, of the signals due to the bridgehead protons H_C or H_D.

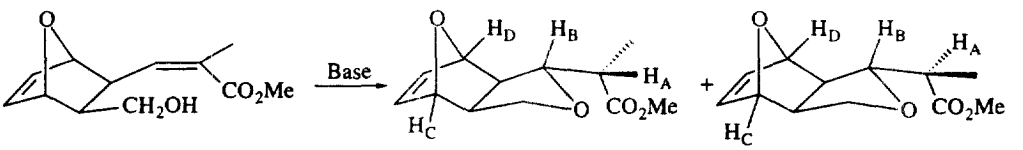
[b] P_4-t-Bu is one member of the phosphazene bases which are extremely strong bases.[18]

with the Dess–Martin periodinane to the aldehyde **11**. Reaction of this aldehyde with the sodium salt of diphenoxy phosphonopropionate[16] led selectively to the (*Z*)-α,β-unsaturated ester **12** (*Z*/*E*=90/10) which, in acidic medium, was converted to the diol **13**.



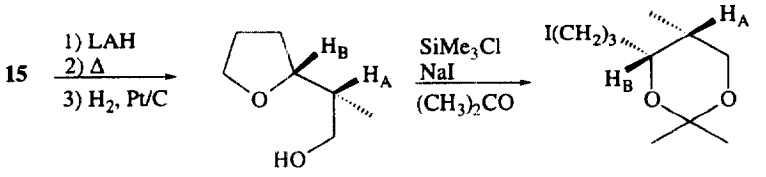
As expected, the Michael cyclization of **13** in the presence of benzyltrimethylammonium methoxide (Triton B) was highly stereoselective with respect to the *cis* configuration around the tetrahydrofuran ring. However, as already observed in similar cases[17] the configuration of the carbon bearing the methyl and the carbomethoxy groups was not controlled and a 1:1 mixture of stereomers was obtained. This lack of selectivity was found totally independent from the *E* or *Z* stereochemistry of the starting olefinic ester **13**.

In order to improve the selectivity of this reaction in favour of the required diastereoisomers, various reaction conditions were tried for the cyclization of the model system **14** and the results are gathered in Table 1.



14 (racemic) **15** **15'**

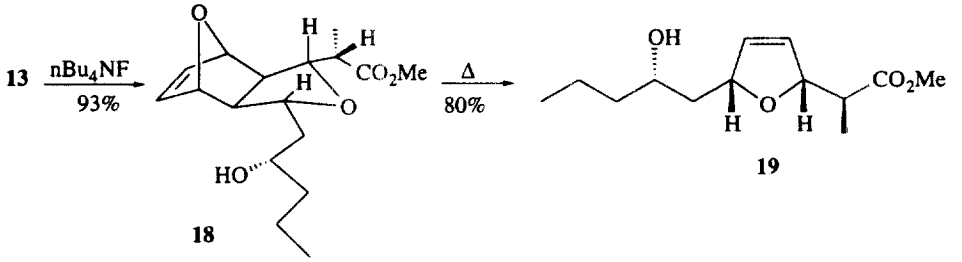
The relative configuration of the two new asymmetric carbons in **15** has been assigned by ^1H NMR spectroscopy after conversion of compound **15** into the acetonide **17**. Thus, reduction of the ester group followed by retro Diels–Alder reaction and catalytic hydrogenation led to the tetrahydrofuran **16**. Ring opening of **16** with trimethylsilyliodide generated *in situ* in the presence of acetone[19] gave rise to the acetonide **17**.



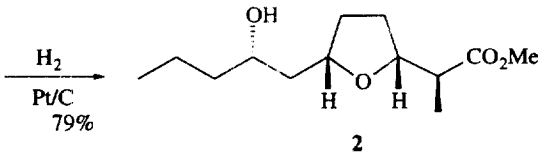
16 17

The value of the coupling constant $J_{H_A-H_B}$=2.6 Hz indicates a *cis* axial-equatorial relationship between the two protons H_A and H_B which is the stereochemistry required for our synthesis.

As shown in Table 1 (entries 4 and 5) a good selectivity in favour of the stereomer **15** was observed when the Michael reaction was catalyzed with the fluoride ion.[20] Under the same conditions, the cyclization of the α,β-unsaturated ester **13**, catalyzed by tetra-n-butylammonium fluoride appeared to be much more stereoselective and the desired tricyclic stereomer **18** was predominantly formed together with a very small amount of the wrong diastereomer (de=90%). No good explanation has been found to date for such selectivity.



18 19



2

Heated under flash-thermolysis conditions (400°C, 10^{-3} torr), the compound **18** underwent retro cycloaddition to furnish the dihydrofuran **19** which, after catalytic hydrogenation afforded the C_1'C_{11}' fragment **2** of pamamycin-607. The spectral data of **2** were in total agreement with the ones already reported.[7b] The value of its specific rotation was found to be higher than the value reported: $[\alpha]_D^{20}$ +30.0 (c 1.06, $CHCl_3$). Lit.[7b]: $[\alpha]_D^{20}$ +20.3 (c 0.012, $CHCl_3$).

In summary, an efficient synthesis of the southern part **2** of pamamycin-607 has been achieved in 13 steps (10.4% overall yield) from the hydroxy acetate **3** and compares very favourably with the reported syntheses. An approach to the C_1C_{18} fragment of this antibiotic is currently under investigation.

Experimental section

General

IR spectra were recorded on a Perkin–Elmer 682 spectrophotometer. NMR spectra were recorded on a Bruker AM 250 or AC 200 spectrometer with tetramethylsilane as an internal standard. Mass spectra were obtained with a GC–MS R.10-10 spectrometer. Optical rotations were measured on a Perkin–Elmer 241 polarimeter. All reactions were carried out under an inert atmosphere of argon and monitored by thin-layer chromatography (TLC). TLC was performed on Merck silica gel 60F-254 precoated on glass.

(1S,2S,3R,4R)-2-Acetoxymethyl-3-t-butyldimethylsilyloxymethyl-7-oxabicyclo[2.2.1]-hept-5-ene **4**

To a solution of hydroxyacetate **3** (5.95 g, 30 mmol) and imidazole (4.51 g, 75 mmol) in DMF (50 mL) was added dropwise a solution of ClTBDMS (4.97 g, 33 mmol) in DMF (50 mL). The

mixture was stirred for 1 h at room temperature and poured into water (75 mL). The aqueous phase was extracted with ether (3×150 mL). The combined organic layers were dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (eluent: petroleum ether/ether=50/50) to give 8.88 g (95%) of **4** as a colourless oil. $[\alpha]_D^{20}$ +11 (c 1.07, $CHCl_3$); IR (neat) 3095, 1755 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.05 (s, 6H), 0.91 (s, 9H), 1.88 (m, 2H), 2.09 (s, 3H), 3.54 (t, J=8.5 Hz, 1H), 3.74 (m, 1H), 3.93 (t, J=10.5 Hz, 1H), 4.32 (m, 1H), 4.79 (s, 1H), 4.87 (s, 1H), 6.36 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ −5.7, 17.9, 20.7, 25.6, 38.7, 42.3, 61.8, 63.8, 79.9, 80.1, 134.8, 135.6, 170.4; CIMS (NH_3) m/z (relative intensity): 330 (MNH_4^+, 88), 313 (MH^+, 100), 312 (M^+, 31), 133 (24), 116 (56). Anal. calcd for $C_{16}H_{28}O_4Si$: C, 61.50; H, 9.03. Found: C, 61.28; H, 9.17.

(1S,2S,3R,4R)-2-Hydroxymethyl-3-t-butyldimethylsilyloxymethyl-7-oxabicyclo[2.2.1]-hept-5-ene **5**

To a solution of acetate **4** (2.70 g, 8.64 mmol) in methanol (50 mL) was added an aqueous solution of 1 M KOH (864 μL, 0.864 mmol). The mixture was stirred for 1 h at room temperature then neutralised with 0.1 M HCl and concentrated *in vacuo*. The oily residue was diluted with ether (50 mL), washed with water (5 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: petroleum ether/ether=70/30) to give 2.31 g (99%) of alcohol **5** as a colourless oil. $[\alpha]_D^{20}$ +23 (c 1.11, $CHCl_3$); IR (neat) 3400, 3080 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.10 (s, 6H), 0.91 (s, 9H), 1.94 (m, 2H), 3.46 (m, 1H), 3.70 (m, 1H), 3.83 (m, 3H), 4.66 (s, 1H), 4.71 (s, 1H), 6.41 (m, 2H); ^{13}C NMR (63 MHz, $CDCl_3$) δ −5.7, −5.6, 18.0, 25.6, 42.4, 42.5, 61.9, 63.2, 80.6, 80.9, 135.2, 135.7; CIMS (NH_3) m/z (relative intensity): 271 (MH^+, 100), 195 (11), 183 (12), 145 (41), 139 (15), 121 (14). Anal. calcd for $C_{14}H_{26}O_3Si$: C, 62.18; H, 9.69. Found: C, 62.20; H, 9.58.

(1S,2R,3R,4R)-2-Formyl-3-t-butyldimethylsilyloxymethyl-7-oxabicyclo[2.2.1]-hept-5-ene **6**

To a solution of alcohol **5** (2.30 g, 8.5 mmol) in CH_2Cl_2 (85 mL) at 0°C was added Dess–Martin periodinane (4.3 g, 10.4 mmol). The mixture was stirred for 1 h and poured into ether (200 mL). The ethereal solution was washed successively with 1 M $Na_2S_2O_3$ (20 mL), $NaHCO_3$ (20 mL) and water (20 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel with petroleum ether/ether=50/50 as eluent to give 1.96 g (86%) of aldehyde **6** as a colourless oil. $[\alpha]_D^{20}$ +43 (c 1.13, $CHCl_3$); IR (neat) 3100, 1725 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.05 (s, 6H), 0.88 (s, 9H), 2.22 (q, J=8.0 Hz, 1H), 2.38 (dd, J=4.6, 8.4 Hz, 1H), 3.72 (d, J=8 Hz, 2H), 4.89 (s, 1H), 5.13 (s, 1H), 6.37 (m, 1H), 6.48 (m, 1H), 9.68 (d, J=4.7 Hz, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ −6.0, 17.6, 25.3, 45.5, 51.2, 62.1, 78.8, 78.9, 134.2, 136.3, 202.5; CIMS (NH_3) m/z (relative intensity): 269 (MH^+, 17), 201 (23), 130 (100). Anal. calcd for $C_{14}H_{24}O_3Si$: C, 62.64; H, 9.01. Found: C, 62.54; H, 9.11.

(1S,2S,3R,4R,1'R)-2-(1'-Hydroxy-3-oxohexyl)-3-t-butyldimethylsilyloxymethyl-7-oxabicyclo[2.2.1]-hept-5-ene **7**

To a solution of lithium diisopropylamide [prepared from diisopropylamine (1.11 g, 11 mmol) in THF (20 mL) and 1.55 M BuLi in hexane (6.45 mL, 10 mmol) at 0°C] was added at −78°C pentan-2-one (805 mg, 9.35 mmol) in THF (10 mL). The mixture was stirred for 30 min and a solution of aldehyde **6** (1.93 g, 7.19 mmol) in THF (20 mL) was added dropwise. The mixture was stirred at −78°C for 1 h. The reaction was quenched with saturated aqueous ammonium chloride and the mixture was allowed to warm to room temperature. The mixture was extracted with ether (3×50 mL) and dichloromethane (50 mL) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (petroleum ether/ether=50/50) to give after two chromatographies 1.66 g (65%) of aldol **7** as a colourless oil and 185 mg (7%) of a mixture of **7** and its stereomer.

7: $[\alpha]_D^{20}$ +7.3 (c 1.21, $CHCl_3$); IR (neat) 3440, 3095, 1740 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.10 (s, 6H), 0.91 (s, 9H), 0.93 (t, J=7.0 Hz, 3H), 1.64 (m, 2H), 1.76 (dd, J=7.7, 9.7 Hz, 1H), 1.96 (m,

1H), 2.51 (t, J=7.3 Hz, 2H), 2.59 (dd, J=8.7, 15.5 Hz, 1H), 2.78 (dd, J=2.8, 15.5 Hz, 1H), 3.81 (dd, J=6.3, 10.2 Hz, 1H), 4.08 (dd, J=8.7, 10.2 Hz, 1H), 4.20 (m, 1H), 4.46 (d, J=1.8 Hz, 1H), 4.68 (s, 1H), 4.73 (s, 1H), 6.39 (m, 2H); ^{13}C NMR (63 MHz, $CDCl_3$) δ −5.7, −5.6, 13.5, 16.7, 18.0, 25.6, 42.8, 45.5, 47.7, 48.4, 64.1, 67.0, 80.4, 81.2, 135.0, 136.3, 210.8; CIMS (NH_3) m/z (relative intensity): 355 (MH^+, 100), 269 (34), 201 (98), 137 (13), 104 (26). Anal. calcd for $C_{19}H_{34}O_4Si$: C, 64.36; H, 9.67. Found: C, 64.57; H, 9.71.

(1S,2S,3R,4R,1'R,3'S)-2-(1',3'-Dihydroxyhexyl)-3-t-butyldimethylsilyloxymethyl-7-oxabicyclo [2.2.1]-hept-5-ene **8**

To a solution of tetramethylammonium triacetoxy borohydride (4.94 g, 18.8 mmol) in anhydrous acetonitrile (15 mL) was added anhydrous acetic acid (15 mL) and the mixture was stirred at room temperature for 30 min. The mixture was cooled to −40°C, and a solution of aldol **7** (1.33 g, 3.75 mmol) in anhydrous acetonitrile was added dropwise. The mixture was stirred at −40°C for 18 h. The reaction was quenched with aqueous sodium potassium tartrate (0.5 N) (40 mL) and the mixture was allowed to warm slowly to room temperature. The solution was diluted with dichloromethane (60 mL) and washed with aqueous saturated sodium bicarbonate (50 mL). The aqueous layer was extracted with dichloromethane (4×50 mL), and the combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (ethylacetate/CH_2Cl_2=20/80) to give 90 mg of pure diol *syn*, 76 mg of a mixture of *syn* and *anti* diastereomers and 909 mg (68%) of pure diol *anti* **8** (81% total yield) as a colourless oil. **8**: $[\alpha]_D^{20}$ +18 (c 1.035, $CHCl_3$); IR (neat) 3420, 3090, 3020 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.12 (s, 6H), 0.91 (s, 9H), 0.95 (t, J=6.9 Hz, 3H), 1.35–1.55 (m, 4H), 1.75–2.08 (m, 4H), 3.59 (br s, 1H), 3.95 (m, 3H), 4.12 (m, 1H), 4.60 (s, 1H), 4.71 (s, 1H), 5.25 (s, 1H), 6.37 (m, 1H), 6.44 (m, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ −5.8, −5.7, 13.9, 17.9, 18.8, 25.6, 39.4, 40.5, 42.6, 47.9, 64.7, 67.7, 68.5, 80.5, 81.4, 134.7, 136.5; CIMS (NH_3) m/z (relative intensity): 357 (MH^+, 100). Anal. calcd for $C_{19}H_{36}O_4Si$: C, 64.00; H, 10.18. Found: C, 64.29; H, 10.18.

(1S,2S,3R,4R,1'R,3'S)-2-(4',6'-Dioxa-5',5'-dimethyl-3'-propylcyclohexyl)-3- t-butyldimethylsilyl oxymethyl-7-oxabicyclo[2.2.1]-hept-5-ene **9**

To a solution of diol **8** (856 mg, 2.40 mmol) in dichloromethane (40 mL) was added pyridinium paratoluenesulfonate (20 mg) and 2,2-dimethoxypropane (10 mL), and the solution was stirred at room temperature for 2 h. The mixture was washed with aqueous saturated sodium bicarbonate (10 mL) and brine (10 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (petroleum ether/ether=20/80) to give 896 mg of **9** (94%) as a colourless oil. $[\alpha]_D^{20}$ +3.0 (c 0.955, $CHCl_3$); IR (neat) 3090, 3000 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.06 (s, 3H), 0.07 (s, 3H), 0.91 (s, 9H), 0.92 (d, J=6.9 Hz, 3H), 1.33 (s, 3H), 1.35 (s, 3H), 1.38–1.55 (m, 4H), 1.60–1.88 (m, 4H), 3.48 (dd, J=9.6, 11.2 Hz, 1H), 3.74 (m, 2H), 4.18 (dd, J=4.1, 9.5 Hz, 1H), 4.66 (s, 1H), 5.01 (s, 1H), 6.36 (m, 2H); ^{13}C NMR (63 MHz, $CDCl_3$) δ −5.4, −5.3, 13.9, 18.3, 18.5, 24.4, 24.8, 25.9, 37.8, 39.4, 42.5, 46.7, 62.7, 66.0, 66.1, 79.1, 80.3, 100.1, 135.6, 135.7; CIMS (NH_3) m/z (relative intensity): 397 (MH^+, 5), 341 (14), 340 (40), 339 (100), 330 (27), 329 (75), 189 (10). Anal. calcd for $C_{22}H_{40}O_4Si$: C, 66.62; H, 10.17. Found: C, 66.77; H, 10.01.

(1S,2S,3R,4R,1'R,3'S)-2-(4',6'-Dioxa-5',5'-dimethyl-3'-propylcyclohexyl)-3-hydroxymethyl-7-oxabicyclo[2.2.1]-hept-5-ene **10**

To a solution of silylether **9** (896 mg, 2.26 mmol) in THF (20 mL) cooled at 0°C was added dropwise a solution of tetrabutylammonium fluoride 1 M in THF (4.5 mL, 4.5 mmol). The solution was stirred for 2 h, allowed to warm to room temperature, concentrated *in vacuo*, diluted with ether (20 mL) and washed with water (20 mL). The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (ethylacetate/petroleum ether=40/60) to give 609 mg (95%) of alcohol **10** as a colourless oil. $[\alpha]_D^{20}$ +39.7 (c 1.02, $CHCl_3$); IR (neat) 3500, 3110 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.93 (t, J=7.0 Hz, 3H), 1.30–1.55 (m with two singlets at

1.32 and 1.44, 10H), 1.58–1.98 (m, 4H), 3.40 (dd, 1H, J=2.3, 10.1 Hz, 1H), 3.69 (m, 1H), 3.77–3.90 (m, 2H), 3.98 (m, 1H), 4.69 (s, 1H), 4.72 (s, 1H), 6.35 (m, 1H), 6.45 (m, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 13.6, 18.2, 23.6, 24.5, 37.4, 39.0, 43.2, 46.6, 62.0, 66.2, 66.8, 79.3, 81.1, 100.3, 134.9, 136.0;

CIMS (NH_3) m/z (relative intensity): 300 (MNH_4^+, 10), 283 (MH^+, 12), 243 (16), 242 (30), 226 (44), 225 (100), 197 (24), 139 (13). Anal. calcd for $C_{16}H_{26}O_4$: C, 68.06; H, 9.28. Found: C, 67.93; H, 9.18.

(1S,2S,3S,4R,1′R,3′S)-2-(4′,6′-Dioxa-5′,5′-dimethyl-3′-propylcyclohexyl)-3-formyl-7-oxabicyclo [2.2.1]-hept-5-ene ***11***

To a solution of alcohol **10** (609 mg, 2.154 mmol) in anhydrous dichloromethane (30 mL) and pyridine (344 mg, 4.3 mmol) cooled at 0°C was added Dess–Martin periodinane (1.3 g, 3.02 mmol) in small portions. The mixture was stirred for 45 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 over magnesium sulfate, concentrated under reduced pressure.

The residue was purified by flash chromatography on silica gel (petroleum ether/ether=50/50) to give 442 mg (73%) of aldehyde **11** as a colourless oil. $[\alpha]_D^{20}$ −18 (c 1.12, $CHCl_3$); IR (neat) 3100, 1730 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.92 (t, J=7.0 Hz, 3H), 1.2–2.55 (m with two singlets at 1.28 and 1.29, 10H), 1.62–1.73 (m, 1H), 1.83–1.93 (m, 1H), 2.07 (dd, J=8.1, 10.6 Hz, 1H), 2.42 (dd, J=5.0, 8.1 Hz, 1H), 3.81 (m, 1H), 3.93 (m, 1H), 4.79 (s, 1H), 5.05 (s, 1H), 6.39 (m, 1H), 6.46 (m, 1H), 9.65 (d, J=5.0 Hz, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 13.5, 18.1, 23.9, 24.3, 37.4, 38.2, 49.6, 51.3, 65.5, 65.7, 78.5, 79.5, 100.1, 134.9, 136.4, 202.1; CIMS (NH_3) m/z (relative intensity): 281 (MH^+, 22), 214 (19), 213 (100), 195 (14), 172 (15), 155 (57), 154 (13), 137 (82), 136 (10). Anal. calcd for $C_{16}H_{24}O_4$: C, 68.54; H, 8.63. Found: C, 69.15; H, 8.79.

(1S,2S,3S,4R,1′R,3′S)-2-(4′,6′-Dioxa-5′,5′-dimethyl-3′-propylcyclohexyl)-3-(2″-carbomethoxyprop-1″-enyl)-7-oxabicyclo[2.2.1]-hept-5-ene ***12***

To a suspension of NaH (50 mg, 2.08 mmol) in anhydrous THF (0.5 mL) cooled at −78°C was added dropwise a solution of methyldiphenoxyphosphonopropionate (606 mg, 1.89 mmol) in THF (1 mL). The mixture was stirred for 30 min and a solution of aldehyde **11** (442 mg, 1.58 mmol) in THF (1 mL) was added. The reaction mixture was stirred at −78°C for 1 h then allowed to warm slowly at 0°C in 4 h. The reaction mixture was quenched with saturated aqueous ammonium chloride (4 mL). The aqueous layers were extracted with ether (3×10 mL). The combined organic layers were dried over magnesium sulfate and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (petroleum ether/ether: 60/40) to give 440 mg (80%) of olefin **12** (*Z*/*E*=90/10) as a colourless oil. The spectral data for (*Z*)**12** are the following; IR (neat) 3090, 1725, 1650 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.92 (t, J=7.0 Hz, 3H), 1.28 (s, 6H), 1.30–1.52 (m, 4H), 1.55–1.85 (m, 2H), 1.91 (m, 1H), 1.94 (s, 3H), 3.37 (dd, J=8.1, 10.5 Hz, 1H), 3.73 (s, 3H), 3.75–3.90 (m, 2H), 4.63 (s, 1H), 4.80 (s, 1H), 6.00 (dd, J=1.4, 10.6 Hz, 1H), 6.41 (m, 2H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 13.7, 18.3, 20.7, 24.3, 24.5, 37.6, 37.9, 39.3, 48.5, 51.0, 65.7, 66.0, 78.9, 84.2, 99.9, 129.2, 134.8, 136.6, 136.8, 144.3, 167.8; CIMS (NH_3) m/z (relative intensity): 351 (MH^+, 31), 293 (62), 284 (25), 283 (100), 225 (58), 224 (16), 207 (24), 126 (19).

(1S,2S,3S,4R,1′R,3′S)-2-(1′,3′-Dihydroxyhexyl)-3-(2″-carbomethoxyprop-1″-enyl)-7-oxabicyclo [2.2.1]-hept-5-ene ***13***

To a suspension of **12** (420 mg, 1.2 mmol) in THF (20 mL) cooled at 0°C was added a solution of hydrochloric acid 1 N (12 mL, 12 mmol) and the reaction mixture was stirred for 1 h. Solid sodium hydrogenocarbonate was added slowly till neutrality. The mixture was extracted with ether (3×20 mL) and dichloromethane (1×20 mL). The combined organic layers were dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (CH_2Cl_2/methanol=95/5) to give 350 mg (94%) of diol **13** (*Z*/*E*=90/10) as a colourless oil. The spectral

data for (*Z*)**13** are the following; IR (neat) 3440, 3090, 1725, 1650 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.95 (t, J=7.0 Hz, 3H), 1.30–1.60 (m, 4H), 1.75 (m, 2H), 2.00 (d, J=1.4 Hz, 3H), 2.06 (dd, J=8.0, 9.5 Hz, 1H), 3.03 (dd, J=8.0, 10.6 Hz, 1H), 3.13 (d, J=4.0 Hz, 1H), 3.47 (s, 1H), 3.78 (s, 3H), 3.93 (m, 2H), 4.64 (s, 1H), 4.79 (s, 1H), 6.07 (dd, J=1.4, 10.6 Hz, 1H), 6.32 (m, 1H), 6.48 (m, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 14.0, 18.9, 20.2, 39.5, 40.7, 40.8, 50.9, 51.9, 68.5, 68.9, 80.0, 83.7, 129.3, 134.1, 137.4, 143.2, 169.6; CIMS (NH_3) m/z (relative intensity): 311 (MH^+, 100), 225 (12), 177 (13), 172 (11), 171 (16), 169 (12), 155 (19), 125 (11).

(1S,2S,3R,5R,6R,7R,3'R,2''S)-3-(2'-Hydroxypentyl-5-(2''-carbomethoxy-1''-propyl)-4,10-dioxa tricyclo[5.2.1.0^{2,6}]dec-8-ene ***18***

To a solution of diol **13** (345 mg, 1.11 mmol) in anhydrous THF (15 mL), cooled at 0°C, was added dropwise a solution of 1 M tetrabutylammonium fluoride in THF (1.1 mL, 1.1 mmol). The mixture was stirred for 1 h, concentrated *in vacuo*, diluted with ether (25 mL) and washed with a saturated aqueous solution of ammonium chloride. The aqueous layer was extracted with ether (3×10 mL). The combined organic layers were dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by flash chromatography (CH_2Cl_2/methanol=96/4) to give 320 mg (93%) of tricyclic compound **18** as a colourless oil. $[\alpha]_D^{20}$ +32 (c 1.01, $CHCl_3$); IR (neat) 3450, 3090, 1740 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.94 (t, J=6.9 Hz, 3H), 1.27 (d, J=7.1 Hz, 3H), 1.35–1.55 (m, 4H), 1.78 (m, 2H), 2.25 (t, J=7.7 Hz, 1H), 2.36 (t, J=7.3 Hz, 1H), 2.71 (q, J=7.2 Hz, 1H), 2.78 (d, J=4.5 Hz, 1H), 3.71 (s, 3H), 3.73 (t, J=7.3 Hz, 1H), 3.87 (m, 2H), 4.68 (s, 1H), 4.74 (s, 1H), 6.37 (m, 2H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 13.9, 14.1, 18.6, 39.4, 40.3, 43.8, 51.4, 52.1, 53.8, 68.4, 79.5, 79.9, 80.8, 82.2, 136.0, 136.2, 174.3; CIMS (NH_3) m/z (relative intensity): 328 (MNH_4^+, 43), 311 (MH^+, 100), 137 (11). Anal. calcd for $C_{17}H_{26}O_5$: C, 65.78; H, 8.44. Found: C, 65.76; H, 8.52.

(2S,3R,6S,8S)-Methyl-8-hydroxy-2-methyl-3,6-epoxy-4-undecenoate ***19***

The tricyclic compound **18** (277 mg, 0.89 mol) was evaporated through a hot horizontal mullite tube (400°, 10^{-3} torr) and the thermolysate was collected on a finger cooled to liquid nitrogen temperature. After warming to room temperature, the finger was washed with ether and the resulting solution was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (eluent: ethylacetate/petroleum ether=50/50) to give 173 mg (80%) of compound **19** as a colourless oil. $[\alpha]_D^{20}$ +25 (c 0.82, $CHCl_3$); IR (neat) 3450, 3090, 1750 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.96 (t, J=6.9 Hz, 3H), 1.20 (d, J=7.1 Hz, 3H), 1.35–1.55 (m, 4H), 1.60–1.75 (m, 2H), 2.38 (d, J=5.2 Hz, 1H), 2.63 (dt, J=5.9, 7.0 Hz, 1H), 3.71 (s, 3H), 3.84 (m, 1H), 4.88–5.10 (m, 2H), 5.80 (m, 1H), 5.86 (m, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 12.5, 13.9, 18.7, 39.6, 42.6, 44.9, 51.5, 68.4, 83.6, 86.9, 127.5, 131.6, 174.3; CIMS (NH_3) m/z (relative intensity): 260 (MNH_4^+, 32), 243 (MH^+, 100), 225 (22), 155 (18), 137 (41). Anal. calcd for $C_{13}H_{22}O_4$: C, 64.44; H, 9.15. Found: C, 64.55; H, 9.26.

(2S,3R,6S,8S)-Methyl-8-hydroxy-2-methyl-3,6-epoxy-4-undecanoate ***2***

A solution of **19** (159 mg, 0.66 mmol) in ethylacetate (6 mL) was hydrogenated over Pt/C 5% (10 mg) at atmospheric pressure for 1 h. After filtration, the catalyst was washed with ethylacetate and the filtrates were concentrated *in vacuo*. The oily residue was purified by flash chromatography on silica gel (eluent: ethylacetate/petroleum ether=40/60) to give 127 mg (79%) of compound **2** as a colourless oil. $[\alpha]_D^{20}$ +30.0 (c 1.06, $CHCl_3$); IR (neat) 3450, 1745 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.93 (t, J=6.9 Hz, 3H), 1.22 (d, J=7.0 Hz, 3H), 1.35–1.80 (m, 8H), 1.98 (m, 2H), 2.59 (p, J=7.0 Hz, 1H), 2.79 (d, J=4.4 Hz, 1H), 3.68 (s, 3H), 3.84 (m, 1H), 3.99 (q, J=7.2 Hz, 1H), 4.13 (m, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 13.8, 14.0, 18.9, 28.7, 30.7, 39.4, 41.2, 44.7, 51.5, 68.7, 77.2, 80.4, 174.8; CIMS (NH_3) m/z (relative intensity): 262 (MNH_4^+, 26), 245 (MH^+, 100), 243 (17), 227 (30), 171 (16), 157 (36). Anal. calcd for $C_{13}H_{24}O_4$: C, 63.91; H, 9.90. Found: C, 63.87; H, 9.93.

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