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Synthesis of ω-Saturated 7-Oxabicyclo[2.2.1]heptane Analogues of Thromboxane A_2

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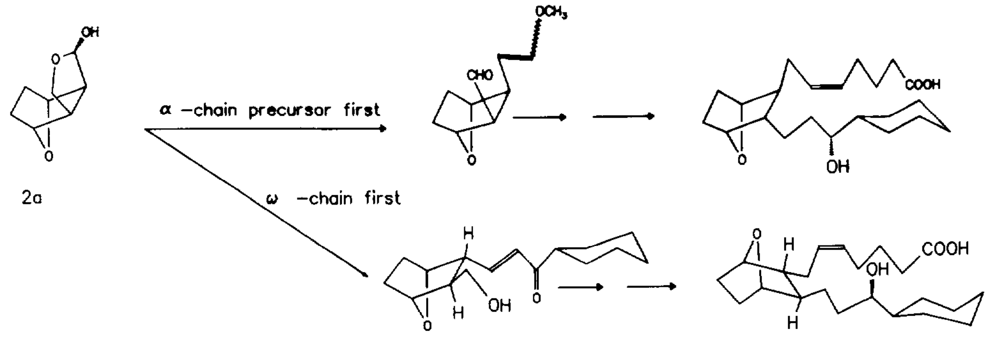
Abstract: A synthesis of 7[3(3*R*-hydroxy-3-cyclohexyl-1-propyl)-7-oxa-1*S*,2*S*,3*S*,4*R*-bicyclo[2.2.1]-heptan-2-yl-5*Z*-heptenoic acid **1**, an ω-chain saturated analogue of Thromboxane A_2 is described. The relative and the absolute configurations of the intermediates and the target compound were determined by 2D FT NMR methods.

The lability of the 2,6-dioxa-bicyclo[3.1.1]heptane ring system characteristic of Thromboxane A_2 has directed research towards alternative ring structures with the aim to obtain more stable new compounds with similar activity. Disubstituted 7-oxa-bicyclo[2.2.1]heptane derivatives are known to be thromboxane and prostaglandin receptor agonists or antagonists depending on the structure and the stereochemistry of the side chains and their orientation on bicyclic ring.[1-3]

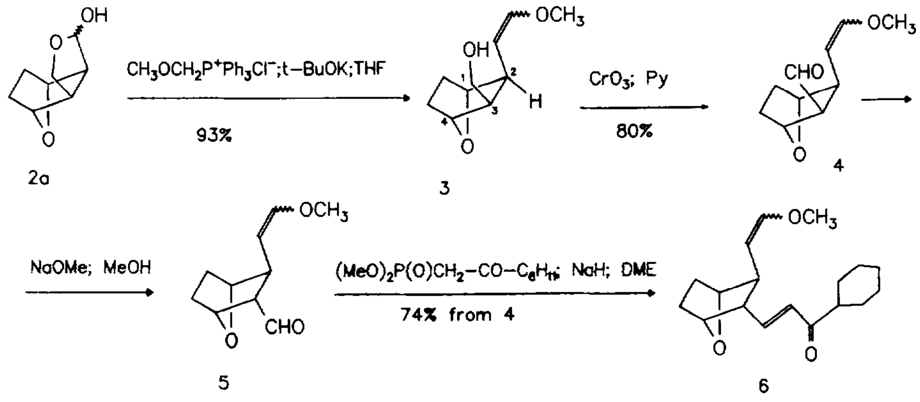
A synthetic scheme for these analogues has been developed by Sprague et al..[4] According to this scheme the absolute configuration of the target thromboxane analogue is determined by the absolute configuration of the starting lactol **2**, and the first step is the introduction of the ω-chain precursor. The enantiomer **2a** is easily separated from the diastereomeric mixture by crystallization of the corresponding menthol derivatives, while separation of the other enantiomer **2b** in pure form is complicated. This makes the route inconvenient for the synthesis of the enantiomeric compounds based on **2b**, for example, for our target compound **1**. These reasons forced us to investigate the possibility of making the synthesis stereoconvergent - in order to obtain the desired compound **1** from the easily available lactol **2a**. We tried to take advantage of the symmetry features of the lactol **2** that enables one to attach one side chain to both enantiofacial sides. Indeed, the consecutive order of addition of α- and ω- side chains (or their precursors) to the intermediate **2a** determines the absolute configuration of the target molecule (for the enantiomer **1** when starting from **2a**, the α-chain or its precursor have to be introduced first "from the lactol side"). In principal, changing the consecutive order of addition of the side chains enables one to get both enantiomers from one enantiomeric lactol **2a** (Scheme 1).

In the case where the target molecule - 7[3(3*R*-hydroxy-3-cyclohexyl-1-propyl)-7-oxa-1*S*,2*S*,3*S*,4*R*-bicyclo[2.2.1]heptan-2-yl-5*Z*-heptenoic acid **1** has saturated ω-chain we have constructed the reaction sequence so that the double bond in ω-chain is reduced before introducing the α-chain double bond. A detailed NMR analysis (^{1}H, ^{13}C, 2D ^{1}H- ^{1}H and ^{1}H-^{13}C COSY) was used for the determination of the relative and the absolute stereochemistry of the compounds throughout the synthetic route.



Scheme 1.

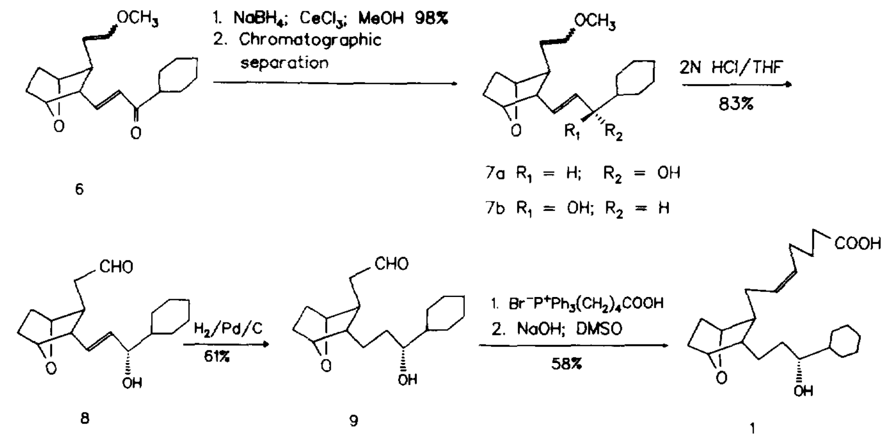
Synthesis. Lactol **2** was synthesized starting from furan and maleic acid anhydride according to the known procedure.[4] Separation of enantiomers followed the method proposed by Sprague et al.[2] to afford **2a**. As it was mentioned before, to get the "right" stereoisomer **1** from **2a**, the α-chain precursor has to be introduced first. So, to lactol **2a** triphenyl methoxymethylene phosphorane was added to afford enol ether **3** in 93% yield. (Scheme 2).



Scheme 2.

To build the α-chain of the molecule, the alcohol group in enol ether **3** was oxidized to aldehyde **4** in 80% yield using CrO_3 in pyridine. The *trans*-configuration of the chains was achieved by isomerization of *cis*-aldehyde **4** to trans-aldehyde **5** by sodium methoxide in methanol. Then the ω-chain precursor was introduced by Wittig-Horner reaction "from anti lactol side" leading to enone **6** in 74% yield (from **4**). The obtained structure already bears the main stereochemical features of the target molecule - the necessary absolute configuration at the side chain connecting carbons and also the required relative *trans*-configuration of the side chain precursors.

Enone **6** was reduced with $NaBH_4$ in the presence of $CeCl_3$ resulting in an 1:1 mixture of *R*- and *S*-allylic alcohols of **7** in 98% yield. (Scheme 3).



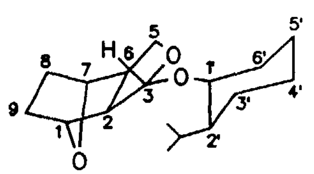
Scheme 3.

After separation of isomers on silica gel (the following diastereomeric pairs formed: *cis*-enol/*R*-alcohol + *trans*-enol/*R*-alcohol and *cis*-enol/*S*-alcohol + *trans*-enol/*S*-alcohol using benzene/iPrOH (80/1) as an eluent and combining the fractions that contain *R*-alcohol (combined **7a**) the enol ether group was hydrolyzed to afford aldehyde **8**. Now it was possible to reduce the double bond in order to get the saturated ω-chain. Reduction of the compound **8** was performed with H_2 using Pd/C as a catalyst to yield aldehyde **9** in 61% yield. The synthesis was completed by generating the α-chain using Wittig reaction to afford the target compound **1** in 58% yield.

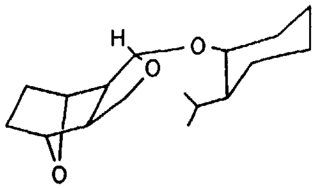
Determination of the relative and the absolute configuration of the reaction intermediates and the target 1 by NMR spectroscopy. The relative and the absolute configurations in the intermediates and target compounds were determined by ^1H and ^{13}C NMR spectroscopy by the use of 2D FT ^1H-^1H and ^1H-^{13}C COSY correlation diagrams.

The absolute configuration of hemiacetal **2** has been determined previously by X-ray analysis[4]. The same result can also be reached more simply from the NMR study of the diastereomeric acetals of **2** with (-)menthol (1*R*,2*S*,5*R*), prepared from racemic **2**. The corresponding ^{13}C and ^1H chemical shifts of these diastereoisomers are presented in Table 1. Large differences in ^{13}C shieldings of C-1 of menthol moiety can be explained by simple conformational analysis along its C-1 - O bond assuming that 1,3-diaxial interactions should be avoided. For the compound **2a** X-ray analysis confirms this postulate.[1] In ^{13}C NMR spectra the gauche interaction with O-atom as compared to C-atom generally results in higher field chemical shifts. For example, in *cis*- and *trans*-isomers of 1-methyl-4-*tert*-butyl cyclohexanol the carbon bearing axial hydroxyl (corresponding to C-3 in isomer A, Table 1) is shifted by 2.3 ppm and C-3,5 (corresponding to 1' in isomer A) by 2.4 ppm to the higher field.[5] This regularity is accentuated in the diastereomeric derivatives of **2a** and **2b**, and thus confirms their stated absolute configurations. In the synthetic route the next crucial point in respect of stereochemistry is the configuration at ω-chain OH-group, appearing in the mixture of enol ethers **7** (*E,Z* at the enol ether double

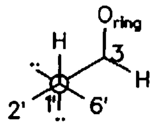
Table 1. C-13 and H-1 chemical shifts in diastereoisomers, prepared from the racemic 3-exo-hydroxy-4,10-dioxatricyclo[5.2.1.0^{2,6}]decane and (-) (1R, 2S,5R)-menthol



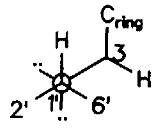
B, from 2b



A, from 2a



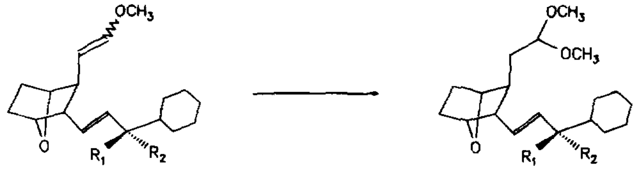
A



B

		4,10-dioxatricyclo[5.2.1.0^{2,6}]decane								1R,2S,5R-menthol						Isopropyl			
		1	2	3	5	6	7	8	9	1'	2'	3'	4'	5'	6'	CH	Me	Me	5-Me
A	C-13	77.98	55.51	98.83	65.07	47.35	79.48	24.23	25.69	73.89	47.72	22.69	34.37	31.29	39.75	25.05	20.97	15.16	22.21
	H-1	4.55	2.69	4.91	3.72 3.68	2.85	4.45	1.70 1.54	1.63 1.56	3.35	1.13	1.57 0.91	1.59 0.77	1.31	2.04 0.75	2.10	0.85	0.72	0.86
B	C-13	77.93	55.66	104.76	64.76	47.25	79.46	24.18	25.61	79.41	48.49	23.20	34.21	31.57	43.29	25.53	21.00	16.24	22.16
	H-1	4.55	2.74	5.05	3.68 3.80	2.85	4.45	1.70 1.53	1.62 1.56	3.22	1.12	1.55 0.92	1.58 0.76	1.35	2.06 0.90	2.02	0.85	0.73	0.84

bond; *R,S* configuration of the carbinol carbon). The assignment of this mixture was simplified by the analysis of a model compound **10** (prepared from **7**) (Scheme 4).



7a R$_1$ = H; R$_2$ = OH

7b R$_1$ = OH; R$_2$ = H

10a R$_1$ = H; R$_2$ = OH

10b R$_1$ = OH; R$_2$ = H

Scheme 4.

The carbon chemical shifts of the two stereoisomers (Table 2) confirm desired stereochemistry- *endo*-α-*exo*-ω-chains from the chemical shifts of C-5 and C-6 of 7-oxa-bicyclo[2.2.1] heptane substituent, assigned by 2D FT spectra. The determination of the absolute configuration of the side chain carbinol carbon is the most serious problem. TLC characteristics based on the behavior of the analogous prostaglandin compounds cannot be transferred to the present case. Additionally, the use of ozonolysis in order to get enantiomers of hexahydromandelic acid was excluded due to low yield giving rise to considerable loss of compounds. So, the absolute configuration at that carbinol carbon was determined by the analysis of 2D FT spectra of the corresponding *R*-MTPA esters (Table 2). Comparison of the chemical shifts of stereoisomeric alcohols **10**, as measured from their mixture, reveals only minor differences not exceeding 0.03 ppm for ^{1}H and 0.19 ppm for ^{13}C NMR spectra, which does not give any key for the assignment of stereoisomers. However, comparison of the effects of *R*-MTPA esters of **10** to the corresponding free alcohol, gives a clear-cut picture of the effects on cyclohexyl moiety. Therefore, the 3'*R* isomer phenyl ring of *R*-MTPA must be oriented towards cyclohexyl ring to induce high field shifts on both ^{1}H and ^{13}C nuclei.[6-8] This phenomenon was observed (Table 2). It should be stressed that the assignment of carbon and proton chemical shifts is possible only by using the method proposed by us for the determination of the absolute configuration.[9] The observed differential effects were used for the assignment of pro-*R* and pro-*S* carbon and hydrogen atoms of cyclohexyl moiety. In *R*-carbinol isomer pro-*R* atoms of cyclohexyl ring must have bigger high field shifts than pro-*S* atoms. Especially noteworthy is 0.21 ppm high field shift of the equatorial proton at pro-*R* C-5' carbon, which is much closer to the aromatic ring of *R*-MTPA than the axial proton.

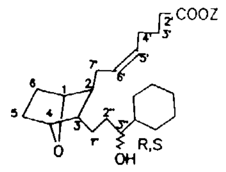
Using the data from compound **10**, four isomers of **7** were assigned by the characteristic differences on carbons C-3,4 and 2' of the alcohols. The configuration of ω-chain carbinol was reconfirmed by preparing and NMR analysis of *R*-MPA esters of **1**. The phenyl ring of *R*-MPA ester, prepared from 3"R alcohol is oriented towards the cyclohexyl ring and must again show shielding of cyclohexyl carbons and protons (Table 3). (It should be mentioned that according to Cahn-Ingold-Prelog *R,S* rules the *R*-carbinol carbon of the compound **10** corresponds to *S*-isomer of the compound **1**. From the other side, phenyl ring of *R*-MPA ester is orientated in the opposite way, as compared to that of *R*-MTPA ester).

The present study shows that a nondestructive method of NMR analysis with the use of 2D FT diagrams correlating proton and carbon chemical shifts can be used for the absolute determination of configuration around quite crowded chiral centers. Full assignment of carbon and proton chemical shifts enables us to compare phenyl

Table 2. C-13 and H-1 chemical shifts of stereoisomeric acetals 10 and their *R*-MTPA esters

		1	2	3	4	5	6	1'	2'	3'	4'	5'		6'		7'	1"	2"
10a(3'*R*)	**C-13**	79.61	46.20	53.70	82.28	30.18	23.78	135.55	130.70	77.27	43.65	28.65	28.84	26.03	26.11	26.50	33.82	103.76
	H-1	4.46	1.89	1.83	4.20	1.43 1.71	1.60 1.75	5.57	5.42	3.76	1.36	0.97 1.86	0.96 1.66	1.22 1.75	1.21 1.73	1.14 1.66	1.67 1.70	4.34
10a(3'*R*)-*R*-MTPA	**C-13**	79.53	46.09	53.53	81.84	30.15	23.79	139.74	124.66	81.55	41.44	28.14	28.48	25.65	25.75	26.17	33.81	103.63
	H-1	4.48	1.88	1.85	4.21	1.43 1.73	1.64 1.76	5.81	5.43	5.25	1.58	0.92 1.65	0.93 1.60	1.16 1.69	1.17 1.69	1.09 1.63	1.67 1.69	4.31
ester-alcohol	**C-13**	-0.08	-0.11	-0.17	-0.44	-0.03	0.01	4.19	-6.04	4.28	-2.21	-0.51	-0.36	-0.38	-0.36	-0.33	-0.01	-0.13
	H-1	0.02	-0.01	0.02	0.01	0.0 0.02	0.04 0.01	0.24	0.01	1.49	0.22	-0.05 -0.21	-0.03 -0.06	-0.06 -0.06	-0.04 -0.04	-0.05 -0.03	0.0 -0.01	-0.03
10b(3'*S*)	**C-13**	79.55	46.26	53.76	82.09	30.12	23.78	135.55	130.54	77.30	43.70	28.58	28.84	26.03	26.11	26.48	33.79	103.71
	H-1	4.46	1.87	1.83	4.23	1.42 1.71	1.60 1.75	5.58	5.41	3.76	1.36	0.97 1.86	0.96 1.66	1.22 1.73	1.21 1.73	1.14 1.66	1.67 1.70	4.33
10b(3'*S*)-*R*-MTPA	**C-13**	79.58	46.17	53.60	81.98	30.20	23.74	139.45	124.60	81.84	41.46	28.50	28.61	25.74	25.82	26.22	33.86	103.84
	H-1	4.48	1.88	1.81	4.17	1.42 1.72	1.64 1.76	5.74	5.33	5.18	1.61	1.00 1.78	0.99 1.68	1.21 1.74	1.21 1.74	1.13 1.67	1.64 1.68	4.27
ester-alcohol	**C-13**	0.03	-0.09	-0.16	-0.11	0.08	-0.04	3.90	-5.94	4.54	-2.24	-0.08	-0.23	-0.29	-0.29	-0.26	0.07	0.13
	H-1	0.02	0.01	-0.02	-0.06	0.0 0.01	0.04 0.01	0.16	-0.08	1.42	0.25	0.03 -0.08	0.03 0.02	-0.01 -0.01	0.0 0.01	-0.01 0.01	-0.03 -0.02	-0.06

Table 3. C-13 and H-1 chemical shifts of 7-[3((3R and S)-hydroxy-3-cyclohexyl-1-propyl)-7-oxa-1S,2S,3S,4S-bicyclo[2.2.1]heptan-2-yl]-5Z-heptenoic acid and their *R*-MPA esters (1a,b)



Isomer		1	2	3	4	5	6	2'	3'	4'	5'	6'	7'	1"	2"	3"	4"	5"		6"		7"
3"*R* alcohol	C-13	79.47	50.04	50.76	81.05	30.11	23.56	33.11	24.51	26.45	129.26	128.88	29.14	30.96	31.66	76.17	42.86	27.53	29.31	26.12	26.31	26.48
	H-1	4.42	1.63	1.09	4.18	1.37 1.72	1.56 1.75	2.34	1.69	2.11	5.36	5.38	1.96 2.30	1.29 1.53	1.41 1.51	3.38	1.32	0.99 1.79	1.07 1.62	1.20 1.76	1.23 1.74	1.13 1.66
3"*R*-*R*-MPA ester	C-13	79.44	49.68	50.37	81.11	30.12	23.61	33.44	24.80	26.74	129.21	128.90	29.23	30.98	29.15	78.62	41.01	27.18	28.80	25.88	26.00	26.18
	H-1	4.38	1.58	1.05	4.09	1.34 1.71	1.55 1.72	2.32	1.70	2.08	5.35	5.33	1.98 2.14	1.22 1.30	1.51	4.74	1.32	0.74 1.39	0.61 1.36	1.02 1.56	1.03 1.54	0.88 1.52
ester-alcohol*	C-13	-0.03	-0.36	-0.39	0.06	0.01	0.05	0.33	0.29	0.29	-0.05	0.02	-0.09	0.02	-2.51	2.45	-1.85	-0.43		-0.28		-0.30
	H-1	-0.04	-0.05	-0.04	-0.09	-0.02	-0.02	-0.02	0.01	-0.03	-0.01	-0.04	-0.07	-0.15	0.05	1.36	0.00	-0.37		-0.20		-0.20
3"S alcohol	C-13	79.37	49.80	50.47	80.97	30.08	23.47	33.31	24.47	26.43	129.17	128.78	29.05	31.05	31.72	76.03	42.91	27.52	29.21	26.07	26.25	26.43
	H-1	4.40	1.61	1.08	4.16	1.34 1.69	1.54 1.73	2.31	1.66	2.08	5.33	5.34	1.90 2.25	1.25 1.51	1.38 1.47	3.33	1.29	0.96 1.77	1.04 1.60	1.18 1.73	1.20 1.71	1.10 1.63
3"*S*-*R*-MPA ester	C-13	79.27	49.58	50.20	80.77	30.06	23.48	33.17	24.56	26.56	129.26	128.88	29.02	30.10	29.08	78.73	40.80	28.00	28.94	25.91	26.01	26.28
	H-1	4.31	1.34	0.88	3.94	1.26 1.65	1.51 1.65	2.36	1.70	2.08	5.36	5.27	1.86 2.07	0.93 0.93	1.39 1.39	4.75	1.47	0.96 1.65	0.91 1.59	1.18 1.72	1.18 1.72	1.09 1.64
ester-alcohol*	C-13	-0.10	-0.32	-0.27	-0.20	-0.02	0.01	-0.14	0.09	0.13	0.09	-0.10	-0.03	-0.95	-2.64	2.70	-2.11	0.11		-0.10		-0.15
	H-1	-0.09	-0.22	-0.20	-0.22	-0.06	-0.06	0.05	0.04	0.00	0.03	-0.07	-0.11	-0.45	-0.04	1.42	0.18	-0.07		-0.01		0.00

*** Mean values for the differences of diastereotopic atoms**

ring anisotropy effects on all positions and demonstrates that the most useful information is obtained not from α-positions to chiral center, but from more distant positions.

EXPERIMENTAL

NMR spectra were recorded on a Bruker AMX-500 spectrometer. The chemical shifts were recorded relative to TMS from solvent ($CDCl_3$) signal. IR spectra were recorded on a Specord IR-75 spectrometer. The elemental analysis was made using Hewlett-Packard 178 element analyzer. TLC was performed using DC-Alufolien Kieselgel 60 (Merck). Merck Silica gel 60 (230-400 mesh) was used for column chromatography. THF and DME were distilled from $LiAlH_4$ before use, DMSO and pyridine from CaH_2, CH_2Cl_2 from P_2O_5 and MeOH from Na.

(1S,2S,3S,4R)-2(E/Z)-Methoxyvinyl-3-hydroxymethyl-7-oxabicyclo[2.2.1]heptane (3). To a stirred solution of *tert*-BuOK (2.35 g, 21 mmol) in THF (45 mL) (methoxymethylene)triphenyl-phosphonium chloride (7.18 g, 21 mmol) was added under argon at 0°C and the mixture was stirred for 20 min. Powdered **2a** (1.08 g, 6.92 mmol) was then added and the mixture was stirred at r.t. for 5 h and then quenched at 0°C with acetic acid (1.3 g in 10 mL of ether). The mixture was poured into saturated NH_4Cl solution (55 mL) and extracted with ether (6 x 30 mL). The extract was washed with saturated $NaHCO_3$ solution (40 mL), with brine (40 mL), dried (Na_2SO_4) and the solvents evaporated. The residue was purified by flash chromatography (silica gel, benzene/i-PrOH 50:1 to 30:1) affording **3** (1.19 g, 93%); IR (film, cm^{-1}) 3500, 2990, 2880, 1670, 1475, 1220, 1165, 1125, 1030, 935, 890, 815. (Calc. for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 65.07; H, 8.77.)

(1S,2S,3R,4R)-3-Formyl-2(E/Z)-methoxyvinyl-7-oxabicyclo[2.2.1]heptane (4). To a solution of pyridine (11.53 g, 146 mmol) in CH_2Cl_2 (380 mL) chromium oxide (7.18 g, 71.8 mmol) was added and the mixture stirred at r.t. under argon for 30 min. Now dry Celite (20 g) and **3** (2.2 g, 11.96 mmol) in CH_2Cl_2 (16 mL) was added and stirring was continued for 30 min. The mixture was filtered and the filtrate was washed with 5% $NaHCO_3$ (3 x 100 mL), 5% $NaHSO_4$ (2 x 250 mL) and 5% $NaHCO_3$ (200 mL), dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography (silica gel, hexane/acetone 20:1) giving **4** (1.74 g, 80%); IR (film, cm^{-1}) 3020, 2870, 2750, 1730, 1670, 1475, 1220, 1165, 1125, 990, 935, 890, 820. (Calc. for $C_{10}H_{14}O_3$: C, 65.92; H, 7.74. Found: C, 65.85; H, 7.78.)

(1S,2S,3S,4R)-3-Formyl-2(E/Z)-Methoxyvinyl-7-oxabicyclo[2.2.1]heptane (5). To a solution of NaOMe (prepared from Na (83 mg) in MeOH (35 mL)) compound **4** (1.74 g, 9.56 mmol) in MeOH (4 mL) was added at 0°C and the mixture was stirred at r.t. for 2 h, and then poured into saturated NH_4Cl solution (500 mL). The reaction mixture was extracted with Et_2O (4 x 150 mL) and the combined extracts were washed with brine (100 mL), dried ($MgSO_4$) and concentrated, giving **5** (1.74 g, 100%). This compound was used in the next step without further purification.

(1R,2S,3S,4S)-2-(3-Oxo-3-cyclohexyl-1(E)-propenyl)-3(E/Z)-methoxyvinyl-7-oxabicyclo[2.2.1]-heptane (6). To a mixture of the anion of dimethyl(2-oxo-2-cyclohexylethyl)phosphonate (prepared by stirring dimethyl-2-oxo-2-cyclohexylethylphosphate (2.29 g, 9.78 mmol) in DME (190 mL) and NaH (55% in oil, 423 mg, 9.68 mmol) under argon for 1 h at r.t.) aldehyde **5** (1.74 g, 9.56 mmol) in DME (20 mL) was added and the resultant

mixture was stirred for 1 h at r.t. The reaction was quenched with acetic acid (0.581 g, 9.68 mmol) and the solvents were removed at 30°C under vacuum. The residue was partitioned between ether (200 mL) and 5% $NaHCO_3$ (200 mL), the ether layer was separated and the water phase extracted with ether (2 x 100 mL). The combined ether extracts were washed with water (200 mL), brine (200 mL), dried (Na_2SO_4) and concentrated. Flash chromatography (silica gel, hexane/acetone 30:1) gave enone **6** (2.066 g,74%); IR (film, cm^{-1}) 3020, 2950, 1705, 1675, 1635, 1465, 1215, 935. (Calc. for $C_{18}H_{26}O_3$: C, 74.45; H, 9.02. Found: C, 74.33; H, 9.03.)

(1R,2S,3S,3'S,4S)-2-(3-Hydroxy-3-cyclohexyl-1(E)-propenyl)-3(E/Z)-methoxyvinyl-7-oxabicyclo-[2.2.1]heptane (7a) and (1R,2S,3S,3'R,4S)-2-(3-hydroxy-3-cyclohexyl-1(E)-propenyl)-3(E/Z)-methoxyvinyl-7-oxabicyclo[2.2.1]heptane (7b). To a solution of **6** (2.066 g, 7.12 mmol) in MeOH (70 mL) $CeCl_3 \cdot 8H_2O$ (2.526 g, 7.12 mmol) was added at 0°C followed by addition of $NaBH_4$ (279 mg, 7.34 mmol) in a 2-min period. After stirring for 7 min, the mixture was poured into saturated NH_4Cl solution (300 mL) and extracted with EtOAc (3 x 150 mL). The combined extracts were washed with water (100 mL), with saturated $NaHCO_3$ (100 mL), brine (100 mL), dried (Na_2SO_4) and concentrated to afford a mixture of **7a** and **7b.** The isomers were separated on silica gel (benzene/i-PrOH 80:1) giving **7a** (1.006 g, 48.4%) and **7b** (1.033 g, 49.7%); (Calc. for $C_{18}H_{28}O_3$: C, 73.93; H, 9.65. Found: C, 73.98; H, 9.65). ^{13}C and ^1H chemical shifts as correlated by 2D FT: **7a E-methoxy**: 82.43 and 4.21 (1); 54.33 and 1.89 (2); 50.00 and 2.30 (3); 80.78 and 4.33 (4); 23.91 and 1.58/1.82 (5); 30.22 and 1.46/1.72 (6); 134.76 and 5.54 (1'); 130.88 and 5.39 (2'); 77.31 and 3.75 (3'); 43.63 and 1.36 (4'); 28.59 and 28.79 (5'); 26.05 and 26.13 (6'); 26.51 (7'); 101.38 and 4.57 (1"); 148.78 and 6.27 (2"); 56.28 and 3.53 (OMe). **Z-methoxy** minor component, only ^{13}C chemical shifts are given: 82.34 (1); 54.69 (2); 46.11 (3); 79.82 (4); 24.28 (5); 30.17 (6); 135.60 (1'); 130.38 (2'); 77.39 (3'); 43.56 (4'); 28.78 and 28.62 (5'); 26.08 and 26.15 (6'); 26.53 (7'); 104.94 (1"); 147.91 (2"); 59.57 (OMe). **7b E-methoxy**: 82.08 and 4.29 (1); 54.45 and 1.90 (2); 50.33 and 2.27 (3); 80.63 and 4.34 (4); 23.89 and 1.58/1.82 (5); 30.20 and 1.46/1.72 (6); 134.62 and 5.55 (1'); 130.63 and 5.38 (2'); 77.44 and 3.75 (3'); 43.60 and 1.36 (4'); 28.70 and 28.77 (5'); 26.02 and 26.08 (6'); 26.51 (7'); 101.34 and 4.59 (1"); 148.75 and 6.26 (2"); 56.34 and 3.53 (OMe). **Z-methoxy**: 82.02 and 4.28 (1); 54.73 and 1.90 (2); 46.23 and 2.82 (3); 79.73 and 4.47 (4); 24.23 and 1.55/1.77 (5); 30.12 and 1.46/1.72 (6); 135.50 and 5.59 (1'); 130.19 and 5.38 (2'); 77.57 and 3.75 (3'); 43.66 and 1.35 (4'); 28.67 and 28.71 (5'); 26.02 and 26.17 (6'); 26.53 (7'); 104.77 and 4.24 (1"); 147.96 and 5.94 (2"); 59.49 and 3.53 (OMe).

(1S,2S,3S,3'R,4R)-[3-(3-Hydroxy-3-cyclohexyl-1(E)-propenyl)-7-oxabicyclo[2.2.1]heptan-2-yl]-acetaldehyde (8). To a mixture of enol ethers **7a** (455 mg, 0.16 mmol) in THF (12 mL) 2N HCl (3 mL) was added and the mixture stirred at r.t. for 6 h. The mixture was then diluted with ether (200 mL), washed with saturated $NaHCO_3$ (50 mL), with brine (50 mL), dried (Na_2SO_4) and the solvents evaporated. The residue was subjected to flash chromatography (silica gel, hexane/acetone 10:2) to afford **8** (360 mg, 83%); IR (film, cm^{-1}) 3500, 3020, 2950, 2740, 1750, 1640, 1460, 1015, 985, 935. (Calc. for $C_{17}H_{26}O_3$: C, 73.35; H, 9.41. Found: C, 73.41; H, 9.43.)

(1S,2S,3S,3'R,4R)-[3-(3-Hydroxy-3-cyclohexyl-1-propyl)-7-oxabicyclo[2.2.1]heptan-2-yl]-acetaldehyde (9). A mixture of aldehyde **8** (360 mg, 1.29 mmol) and 10% Pd/C (70 mg) in EtOH (7 mL) was stirred under an atmospheric pressure of H_2 for 2 h at r.t. After filtration and removing the solvents the residue was purified by flash chromatography (silica gel, benzene/EtOAc 10:4) giving **9** (222 mg, 61%); IR (film, cm^{-1}) 3500, 3020, 2950, 2740, 1750, 1460, 995, 935. (Calc. for $C_{17}H_{28}O_3$: C, 72.82; H, 10.06. Found: C, 72.75; H, 10.06). ^{13}C and

^{1}H chemical shifts as correlated by 2D FT: 78.83 and 4.56 (1); 43.27 and 2.02 (2); 50.66 and 1.14 (3); 80.54 and 4.19 (4); 29.83 and 1.33 (endo)/1.71 (exo) (5); 23.74 and 1.57 (exo)/1.60 (endo) (6); 31.40 and 1.36/1.51 (1'); 32.16 and 1.31/1.47 (2'); 76.07 and 3.30 (3'); 43.45 and 1.28 (4'); 29.21 and 1.04 (ax)/1.61 (eq); 27.57 and 0.97 (ax)/1.76 (eq) (5'); 26.09 and 1.19 (ax)/1.74 (eq); 26.25 and 1.21 (ax)/ 1.73 (eq) (6'); 26.43 and 1.12 (ax)/1.64 (eq) (7'); 45.94 and 2.43/2.61 (1"); 200.99 and 9.73 (2").

(1S,2S,3S,3'R,4R)-7-[3-(3-Hydroxy-3-cyclohexyl-1-propyl)-7-oxabicyclo[2.2.1]heptan-2-yl]-5(Z)-heptenoic acid (1). A solution of aldehyde **9** (222 mg, 0.79 mmol) in Me_2SO (3 mL) was added to a mixture of ylide prepared from (4-carboxybutyl)triphenylphosphonium bromide (1.054 g, 2.38 mmol) and sodium methylsulfinylmethide (3 mL, 4.76 mmol) and the reaction mixture stirred at r.t. under argon for 1.5 h. The reaction was quenched with water (20 mL) at 0°C, then acidified with 1M $NaHSO_4$ to pH 3-4 and extracted with ether (3 x 80 mL). The extracts were washed with water (50 mL), with brine (50 mL), dried (Na_2SO_4) and concentrated. Purification of the residue on silica gel (hexane/i-PrOH 20:1) gave acid **1** (167 mg, 58%). (Calc. for $C_{22}H_{36}O_4$: C, 72.49; H, 9.95. Found: C,72.37; H, 9.96.)

The same procedure was used to convert **7b** to (1S,2S,3S,3'S,4R)-7-[3-(3-hydroxy-3-cyclohexyl-1-propyl)-7-oxabicyclo[[2.2.1]heptan-2-yl]-5(Z)-heptenoic acid (106 mg, 28% after three step).

Allylic alcohols **7a** (*cis*-enol/3'*R*-alcohol + *trans*-enol/3'*R*-alcohol) and **7b** (*cis*-enol/3'*S*-alcohol + *trans*-enol/3'*S*-alcohol) were separately converted to acetals **10** ($MeOH/CH_2Cl_2$ 1:10, cat. *p*-TsOH) and then to the corresponding (*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (*R*-MTPA) esters. For the structure confirmation, the acid **1** was esterified with ethereal diazomethane and then converted to (*R*)-(-)-α-methoxyphenylacetic acid (*S*-MPA) ester. Also, the corresponding *R*-MPA ester of 3'*S*-isomer of **1** was prepared and analyzed by NMR (Table 1).

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