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Synthesis of the western half of breviones C, D, F and G

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ABSTRACT

The enantioselective synthesis of the diterpenic moiety in the *abeo*-breviano skeleton is reported. The synthesis is carried out starting from 2-methyl-1,3-cyclohexanedione and EVK in eleven steps following a ring-expansion strategy once the tricyclic perhydrophenantrene skeleton has been obtained. A new Tiffeneau–Demjanov rearrangement under dark conditions is reported in which the insertion of the new methylene group is directed towards the most hindered side of the carbonyl group. This result is new and opposite to those reported in the literature under light (filtered or un-filtered wavelengths) conditions where insertion in the less hindered side is usually preferred.

1. Introduction

Phytotoxins are fungal metabolites that have phytotoxic properties and are responsible in part for the deleterious effects produced by fungi in plants. These compounds have attracted interest because of their potential use in agriculture as a source of new herbicides, of which AAL-toxin, phosphinothricin and tentoxin are successful examples.[1] Glufosinate is the synthetic version of phosphinothricin and is one of the most successfully marketed herbicides. Another attractive feature of natural products is that they offer new target sites that are still unexplored and are ready to be used for the development of new herbicides. All of these facts have increased the interest in the total synthesis of these compounds.

Our group reported the isolation from *Penicillium brevicompactum* cv. Dierckx of breviones A–D.[2,3] These compounds represent a new class of mixed-origin metabolites named breviones and provide an interesting goal for synthetic chemists because of their unique structure, which comprises a dihydrofurospiranic ring linked with an aromatic α-pyrone moiety and at least five chiral centres.

To date, this family of compounds includes three structural subgroups that have been named breviane (compounds **1**, **2** and **9**), *abeo*-breviane (**3**–**6**, **8**) and *abeo*-norbreviane (**7**).[3] Brevianes include breviones A and B and lygodinolide (**9**)-isolated from *Lyngodium flexuosum*;[4] *abeo*-brevianes include breviones C and D and the recently disclosed breviones F, G and H isolated from the marine deep sea fungus *Penicillium* spp.[5] Finally, the *abeo*-norbreviane E differs in the spiro-fused ring, which has been modified as an oxepane in the terrestrial brevione E (**7**) (Fig. 1).

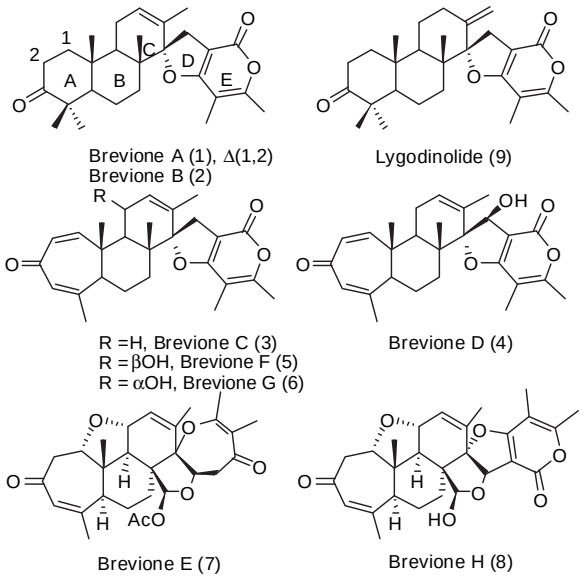

Figure 1. Breviones isolated from fungi and higher plants.

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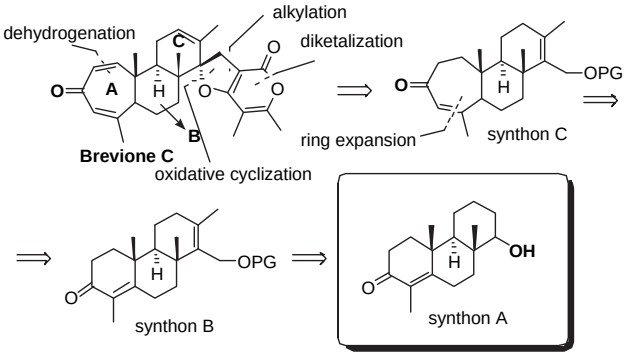
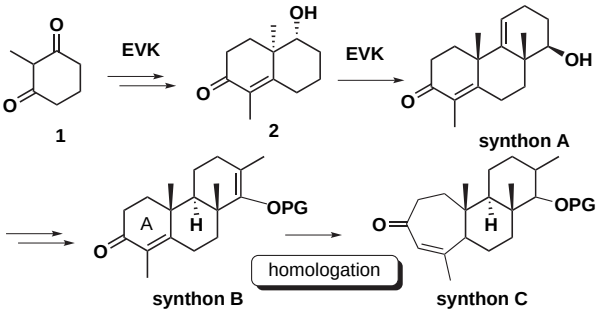
2. Results and discussion

In coincidence with the retrosynthetic analysis of Takikawa for brevione B[6] we envisioned a parallel route for the synthesis of breviones C, D, F and G where the key step is a ring expansion reaction to gain access to the cycloheptane ring (Scheme 1). This analysis allowed us to use synthon B, obtained as an intermediate in the synthesis of breviones A and B, as the starting material for the synthesis of brevione C.



Scheme 1. Retrosynthetic analysis for *abeo*-breviones C and D.

Synthon B is easily obtained in enantiopure form 2-methylcyclohexanedione and ethyl vinyl ketone[6] and can lead easily to synthon C using a ring-expansion approach. Thus, the homologation of ring A constitutes the main goal of this strategy (Scheme 2).

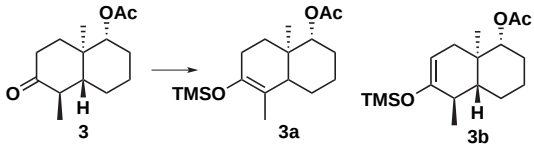


Scheme 2.

There are several methodologies available for ring expansion reactions. The Baeyer–Villiger reaction is one obvious candidate, as the ring opening of the resulting lactone allows homologation of the side chains. Subsequent use, for example, of ring-closing metathesis should lead to the desired seven-membered ring. Transition metals-catalyzed cycloadditions is also another possibility. However, we chose in this case to explore the possibility of expanding the ring in just one step by using carbene chemistry.

Accordingly, we used compound **3** as a model, with the formation of the thermodynamically favoured enol **3a** expected. This would lead to the insertion of the methine group in the correct position. Also, we expected the formation of small amounts of **3b**. Surprisingly, even trace amounts of the silylenol ether could not be detected under the conditions reported in the literature.[7] Only when the solvent was changed to acetonitrile[8] and the temperature raised to 80 °C were we able to isolate the undesired compound **3b** in reasonable amounts (Table 1).

Table 1
Sylilenol ether formation conditions



Conditions	3a	3b
DMF, 2.5 equiv Et_3N, 2.5 equiv TMSCl, 153 °C	—	—
ACN, 1 equiv Et_3N, 6 equiv NaI, 6 equiv TMSCl, a: rt; b: 50 °C; c: 60 °C	—	—
ACN, 1 equiv Et_3N, 6 equiv NaI, 6 equiv TMSCl, 80 °C	—	67%

In view of these adverse preliminary results we decided to perform the homologation using a Lewis acid-catalyzed diazoalkane addition, which have proven to be useful in obtaining cycloheptanones from cyclohexanones following the conditions described by Yang et al.[9] The reaction proceeds via a Tiffeneau–Demjanov type intermediate and oxidative dehydrosylilation of the TMS derivative intermediate in a one pot design experiment.

Even though we were able to scale-up the synthesis of synthon A to a multigram scale, we preferred to optimize the ring expansion methodology using the decalinic intermediate **2**, obtained in due course of the synthesis, as it represents a simplified model of synthon B (Fig. 2). Thus, treatment of the protected decalone **3** with $TMSCHN_2$ followed by Pd-catalyzed dehydrosilylation lead to the two regioisomers of the desired cycloheptenone.

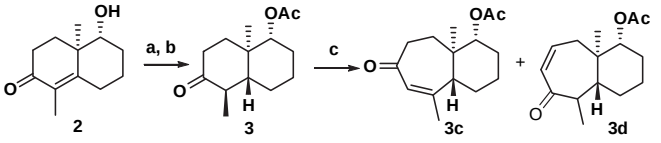


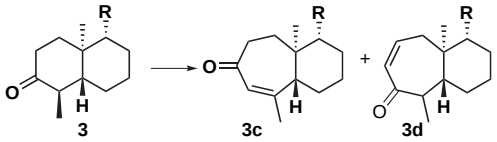
Figure 2. Key: (a) H_2, Ac_2O, 2 atm, 24 h., quant.; (b) dry py, Ac_2O, quant.; (c) (1) $TMSCHN_2$, Me_3Al, DCM; (2) $Pd(OAc)_2$, BQ, Acetonitrile, overall yield for the two steps and the two regioisomers, 58%.

All attempts to perform the reaction with the free alcohol resulted in degradation of the starting material. Consequently, the alcohol was derivatized using a variety of protecting groups and the reaction was optimized under the conditions shown in Figure 2 and Table 2. The best overall yield (58%) involved the use of acetate as protecting group (Table 2, entry 2) but with the incorrect regioisomer **3d** being favoured. Only when MOM was chosen as protective group the desired regioisomer **3c** could be obtained in higher amounts than **3d**. The results obtained are in good accordance with those in the literature reporting that an equimolecular mixture of both regioisomers is usually obtained and that the reaction is sensitive to substituent effects.[9]

Despite these initial adverse results we turned then our attention to the main aim: the synthesis of the western part of *abeo*-breviones C, D, F and G. We recently accessed synthon B during the synthesis of the same part of breviones A and B. Consequently, the use of synthon A as the starting material would lead us to the step prior to the ring expansion reaction (Fig. 3).

Compound **4** was obtained during the synthesis of breviones A and B.[10] Homologation of the MOM protected derivative of **4** only proceeded when complete reduction of the double bonds was carried out. Subsequent scale-up of the reaction also allowed detecting besides the expected compound **5** trace amounts of compounds resulting from the reduction of the carbonyl group **12** (2,8-diol) and that of the migration of the double bond to render

Table 2
Optimization of ring expansion conditions



R	Reagent	Solvent	Yield
OH	(1)$TMSCHN_2$, Me_3Al (2) $Pd(OAc)_2$ BQ	DCM	**3d**: 10%
OAc	(1)$TMSCHN_2$, Me_3Al (2) $Pd(OAc)_2$ BQ	DCM	**3c**: 15% **3d**: 43%
OTMS	(1)$TMSCHN_2$, Me_3Al (2) $Pd(OAc)_2$ BQ	DCM	**3d**: 6%
	(1)$TMSCHN_2$, Me_3Al (2) $Pd(OAc)_2$ BQ	Toluene	**3d**: 39%
OMOM	(1) $TMSCHN_2$, Me_3Al (2) $Pd(OAc)_2$ BQ	DCM	**3c**: 23% **3d**: 19%

BQ: benzoquinone; DCM: dichloromethane.

the dicarbonilic (2,8-dione) compound **13**. Migration of the double bond in olefin hydrogenation is not uncommon and has been previously reported.[11,12] However, the isomerisation reported herein needs of three consecutive isomerizations or jumpings. Curiously, the intermediates of such process with the double bond in different positions of ring C could not be detected. We could not find examples of such behaviour, being this the first time that has been reported to our knowledge.

The homologation of the MOM derivative **6** was carried out under a variety of conditions (Fig. 3, conditions d, e and f) looking for a higher regioselectivity leading to the correct stereoisomers **7a** or **7c**. Best yields and regioselectivity were obtained using dark conditions (entry e, Fig. 3). This change represents a modification with respect to the method reported[9] and introduces some striking points that need further discussion.

First, the regioselectivity of the reaction changes drastically under dark conditions favouring homologation at the most hindered carbon, while under light conditions the ratio between both regioisomers is the opposite. This is an unexpected result, that is, reported for the first time in this type of reactions. The key step is the pinacolinic-type rearrangement that takes place after addition of the $TMSCHN_2$ to the carbonyl group (Fig. 4). Cleavage of bond 'b' leads the insertion in the most hindered side of the carbonyl group, which corresponds to the natural breviane skeleton. It has been reported that Lewis-catalyzed Tiffeneau–Demjanov rearrangement is sensitive to substituent effect in the α-side chain and, probably, to the Lewis acid.[9] However, no previous reports have been published on the influence of light in this process.

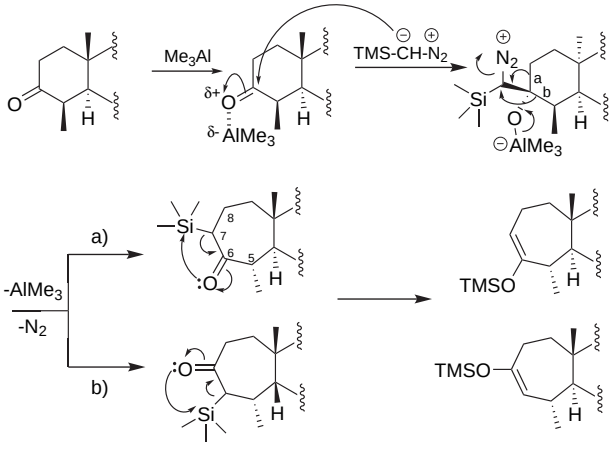


Figure 4. Mechanism for the Tiffeneau–Demjanov rearrangement.

Also, the dehydrosilylation step is strongly influenced by light (entries d, e and f, Fig. 3) and solvent.[13] BQ cannot be excited to the triplet state under dark conditions and direct Pd-catalyzed desilylation instead of β-dehydrosylilation occurs giving rise to the corresponding cycloheptanone. Under light conditions, ^{3}BQ reacts

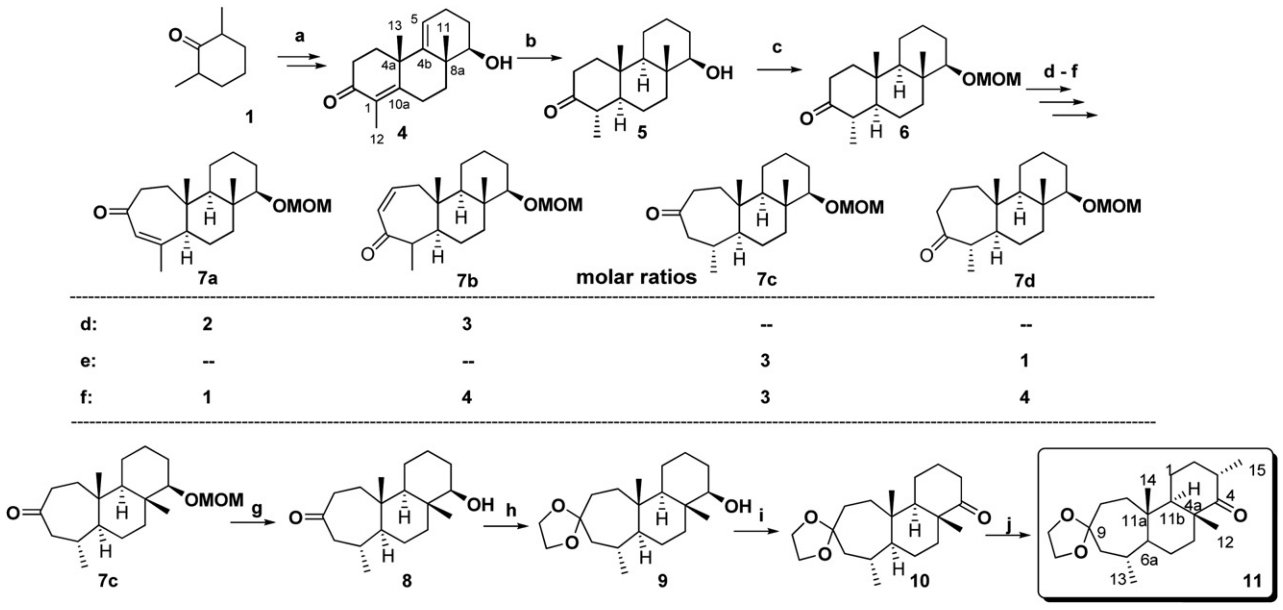


Figure 3. Key: (a) See Ref. 6; overall yield (four steps): 31% (b) See Ref. 10, 85%; (c) ClMOM, DIPEA, DMF, 90%; (d) (1) $TMSCHN_2$, Me_3Al, DCM; (2) $Pd(OAc)_2$, BQ, Acetonitrile, overall yield for the two steps 57%; (e) dark; (1) $TMSCHN_2$, Me_3Al, DCM; (2) $Pd(OAc)_2$, BQ, acetonitrile, overall yield for the two steps 58%; (f) <300 nm (1) $TMSCHN_2$, Me_3Al, DCM; (2) $Pd(OAc)_2$, BQ, acetonitrile, overall yield for the two steps 49%; (g) DCM, 4 Å molecular sieves, TMSBr 81%; (h) ethylene glycol (cat), *p*-TsOH (cat.), DME, 80%; (i) DCM, PDC, 85%; (j) ^{t}BuOK, THF, −10 °C, MeI, 90%. Overall yield of the eleven steps: 5%. Note: reaction conditions in entry (d) lead to compounds **7a** and **7b** in a 2:3 ratio, and so on with the other entries.

with the palladium–silyl enol ether intermediate of the ring expansion leading to the β-dehydrosilylation products.

While wavelength is of crucial importance in excitation of BQ to ^{3}BQ strong solvent modulation has been previously reported when chloranil was used as sensitizer.[13] The joint effect of these two factors should explain why a mixture of saturated and unsaturated carbonyl systems is obtained in entry f, Figure 3 (λ<300 nm). However, the change in the regioselectivity remains yet to be justified but opens a new route to control this reaction.

Using compound **7c** and proceeding as described previously for breviones A and B,[10] we got access to **11** in a stereoselective manner, which is ready for the introduction of the spiranic ring. Indeed, we are currently optimizing the addition of the α-pyrone moiety to finish the enantioselective synthesis of breviones A–D. The absolute configuration of compound **11** was confirmed to correspond to natural breviones through X-ray crystallography (Fig. 5). The refinement was based on low-temperature (90 K) Cu Kα data, resulting in R=0.025. Resonant scattering, principally from the O atoms, resulted in a Flack parameter[14] x=0.06(14) and a Hooft parameter[15] y=0.01(6) for 1452 Bijvoet pairs. This corresponds to a probability of 1.000 that the illustrated configuration is correct.[16]

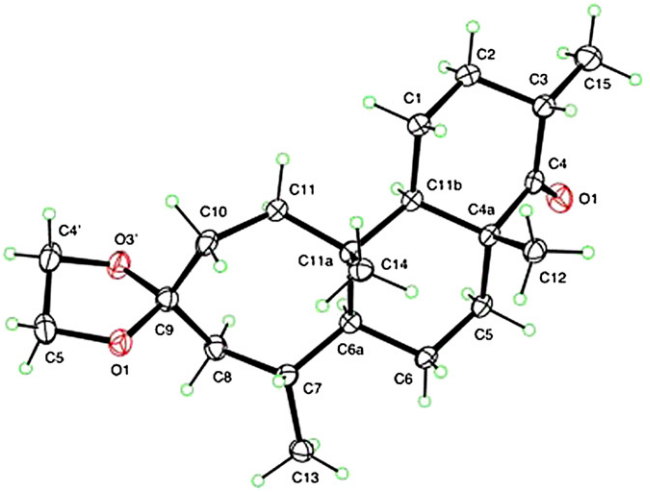


Figure 5. Absolute configuration of compound **11** as obtained from X-ray diffraction, with 50% ellipsoids.

3. Conclusions

We report the enantioselective synthesis of the diterpenic moiety of the *abeo*-breviane skeleton from 2,6-dimethylcyclohexanone and EVK—eleven steps without any racemic resolution—in an overall yield of 5%. Also, new results in the regioselectivity of the Tiffeneau–Demjanov reaction under complete dark conditions are reported.

4. Experimental

4.1. General

All reagents and solvents were used as obtained from commercial suppliers. Solvents were distilled from glass prior to use. Column chromatography was performed on silica gel (35–75 mesh) and TLC analysis was carried out using aluminium-packed precoated silica gel plates. For semi-preparative HPLC, LiChrosorb silica 60 was used in the normal-phase mode with a differential refractometer (RI) in a Hitachi L-6020 HPLC instrument. Preparative HPLC was run in a Prep-Star D1 instrument with a ProStar350 RI detector and a Phenomenex (silica Luna 10 μ) column. ^{1}H and ^{13}C NMR spectra were recorded using a Varian INOVA-400 spectrometer (at 400 MHz and 100 MHz, respectively) using $CDCl_3$ and bencene-d_6 as solvents. The resonance of residual solvent at δ_H 7.25 ppm and δ_H 7.15 ppm in the ^{1}H and δ_C 77.00 ppm and δ_C 128.0 ppm in the ^{13}C spectra for $CDCl_3$ and bencene-d_6, respectively, were used as internal references. Mass spectra were obtained using a VG 1250 or a VG AUTOSPEC instruments at 70 eV. IR spectra were recorded on a Mattson 5020 spectrophotometer. Optical activities were recorded in a Perkin–Elmer 241 polarimeter using the sodium wavelength (λ=520 nm) (cell: 1 dm length, 1 mL) in methanol (Aldrich 99.9% spectral grade).

4.2. Silyl-enol ether 3b

Decalone **3** was obtained enantiomerically pure following the procedure of Hagiwara[17] followed by $NaBH_4$ reduction, Pd/C catalyzed reduction of the double bond and acetylation (acetic anhydride in pyridine). Then, 235 μL of Et_3N (1.8 mmol), 250 mg of NaI (1.8 mmol), and 215 μL (1.8 mmol) of TMSCl were added to a solution of 70 mg (0.3 mmol) of the acetylated decalone **3** dissolved in 5 mL of acetonitrile (ACN) under argon atmosphere. The reaction was stirred at room temperature for 20 min and heated at 80 °C for another 20 min. The reaction mixture was quenched using aqueous $NaHCO_3$ (2.5%) and partitioned using ethyl acetate (3×). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and the organic solvent evaporated in vacuum at 0 °C. The crude of reaction was purified by column chromatography (CC) using a mixture of hexanes(Hx)/ethyl acetate (AcOEt) 10%, yielding **3b** in a 67%.

4.3. Palladium catalyzed hydrogenation (2, 4)

Compound **4** (500 mg) was dissolved in 10 mL of AcOEt and shacked under H_2 atmosphere (3 atm, 6 days) in a GERHARDT (HY 1000 model) hydrogenator. The reaction mixture was then filtered using Celite and the organic solvent evaporated in vacuum. The crude was purified by CC (Hx/AcOEt 30% as eluant) yielding **5** (85%) and trace amounts of **12** and **13**. In the case of compound **2** the hydrogen pressure was of 1 atm and the reaction time of 5 h. The eluant for CC was Hx/AcOEt 50% and the yield for the reduction product was of 85%.

*4.3.1. (1R,2S,4aS,4bR,8R,8aR,10aS)-1,4a,8a-Trimethyltetradecahydrophenanthrene-2,8-diol (**12**).* $C_{17}H_{30}O_2$; amorphous white solid; $[\alpha]_D^{20}$ −10 (*c* 0.1, MeOH); IR $\nu_{max}^{neat,\ KBr}$ cm^{-1}: 3442 (OH, st), 2946 (C–H); HRMS calcd for $C_{17}H_{30}O_2$ 266.2246, found 266.2246; EIMS (70 eV) *m*/*z* (rel int.): 266 $[M]^+$ (22), 248 $[M-H_2O]^+$ (29), 231 $[M-H_2O-HO]^+$ (100), 193 (78), 175 (55), 95 (38). ^{1}H NMR (400 MHz, $CDCl_3$): see Table 3 *J*(Hz): H-2 (5.9, 5.9, 10.5); H-4 (3.5, 3.5, 12.6); H-4′ (5.1, 12.4); H-4b (2.6, 11.9); H-7′ (4.2, 4.2, 11.9); H-8 (4.1, 11.5); H-9 (2.7, 2.7, 12.5), H-9′ (4.1, 4.2, 14.7); H-12 (7.4). ^{13}C NMR (50.3 MHz, $CDCl_3$): see Table 4.

*4.3.2. (1S,4aS,4bR,8aR,10aS)-1,4a,8a-Trimethyldecahydro-phenanthrene-2,8(1H,8aH)-dione (**13**).* $C_{17}H_{26}O_2$; amorphous white solid; $[\alpha]_D^{20}$ +8 (*c* 0.1, MeOH); IR $\nu_{max}^{neat,\ KBr}$ cm^{-1}: 2946 (C–H), 1705 (ν C=O); HRMS calcd for $C_{17}H_{26}O_2$ 262.1933, found 262.1935; EIMS (70 eV) *m*/*z* (rel int.): 262 $[M]^+$ (100), 191 (50), 124 (68), 111 (83), 81 (59), 55 (87). ^{1}H NMR (400 MHz, $CDCl_3$): see Table 3 *J*(Hz): H-1 (6.6); H-4 (0.9, 6.9, 13.1, 15.1); H-7 (6.9, 13.9, 13.9); H-7′ (5.4, 6.8, 15.6); H-9′ (5.0, 15.1, 15.1); H-12 (6.6). ^{13}C NMR (50.3 MHz, $CDCl_3$): see Table 4.

4.4. Acetylations

Acetylations were carried out using the standard methodology consisting of dissolving the compound in 5 mL of dry pyridine and

Table 3
^{1}H NMR chemical shifts (400 MHz, signal of residual solvent centred at δ 7.25 ppm for CH_3Cl and δ 7.15 ppm for C_6H_6)

H	5	6	7a	7b	7c	7d	8	9[a]	10[a]	11[a]	12	13
1	2.24(β) br q	2.26	1.30(β) m	1.24	1.23	1.21	1.24	1.05	1.23 dddd	1.30 m	1.93(α)m	2.26(β)
			1.54(α) m	1.53	1.58	1.48	1.60	1.44	1.47	1.48 dddd		
2	—	—	1.81 m	1.81	1.65(α) ddd	1.76 m	1.68	1.46	1.57	0.89 dddd	3.70(α)ddd	—
					1.17(β) m		1.24	1.18	1.18	1.66		
3	2.28 ddd	2.32	1.40(β) m	1.43	1.37 dddd	1.41 m	1.65	1.32 dddd	2.19 ddd	2.28 ddq	1.56(1H)m	2.33 ddd
	2.41 ddd	2.43	1.74(α) m	1.78	1.75	1.74	1.40	1.50	2.11 dddd			2.44 ddd
4	1.27 ddd	1.26 m	3.04(α) dd	2.98	2.99	2.99	3.12	2.89	—	—	0.92 dd	1.36 m
	2.00 ddd	2.02									1.68 ddd	2.05 ddd
4b	0.76(α) dd	0.80 (α)	—	—	—	—	—	—	—	—	0.69(α)dd	1.12 m
5	1.24 m .50 ddd	1.30	1.08(α) ddd	1.02	1.03 m	1.00	1.06	1.82 m	1.70 (2H)	1.71	1.18(1H)m	1.32 m
		1.53	2.00(β)	1.95	1.94	1.92	1.87			1.77		1.70 m
6	1.36 ddd	1.35 m	1.56(α) br d	1.68 dddd	1.80 m	1.76	1.30(α)	1.06	1.06	1.50	1.74(1H)m	1.54 m
	1.76 dd	1.78 m	1.82(β)	1.32 m	1.80		1.78(β)	1.60	1.49	1.10		2.10 m
6a	—	—	2.51(α) br d	1.37 m	0.97	1.25	0.97	1.16	1.07	1.08	—	—
7	1.43 ddd	1.39	—	2.31(β) dq	1.79 m	2.27 dq	1.81 m	1.77	1.70	1.68	1.36 ddd	2.21
	1.60 ddd	1.74 m									1.61 m	2.57 ddd
8	3.10(α) dd	3.00(α)	5.80 br s	—	2.51(α) dd	—	2.50	1.75	1.66	1.67	3.11(α)dd	—
					2.36(β) dd		2.37	1.97 br d	1.89	1.90 m		
9	1.05 dd	1.05 ddd	—	5.92 d	—	2.56(α)	—	—	—	—	1.24 ddd	1.59
	1.89 ddd	1.98				2.32(β)					1.87 ddd	1.70 m
10	1.25 m	1.21	2.34 (α) ddd	6.19	2.26	1.51 m	2.26 ddd	1.85	1.74(2H) m	1.80 m	1.39(1H) m	1.76
	1.52 dd	1.60	2.42 (β) ddd		2.44	1.68 m	2.44 ddd	1.77 m		1.70		
10a	1.12(α) ddd	1.13(α)	—	—	—	—	—	—	—	—	1.10(α) m	1.12
11	0.91 s	0.96	1.25 (β) m	2.63 ddd	2.00	2.04 m	2.01 ddd	1.54	1.41	1.41	0.81 s	1.18
			2.04 (α) m	2.07br d	1.46 ddd	1.04 m	1.47 ddd	1.64	1.53	1.54		
11b	—	—	0.94 (α) dd	0.82	0.77	0.77	0.77	0.68	0.96	0.95	—	—
12	0.96 d	0.98	0.97 s	0.92	0.93	0.93	0.90	0.88	0.84	0.84	0.86 d	0.99 d
13	1.01 s	1.02	1.88 br s	1.16 d	1.01	1.11	1.01	0.87	0.82	0.83	0.87 s	1.12
14	—		0.85 s	0.81	0.72	0.69	0.73	0.76	0.71	0.73	—	—

H-1′: **6**,**7b**,**7d**: δ 4.55 (d), **7c**: δ 4.54 (d), **6**,**7b**,**7c**,**7d**: δ 4.67 (d); **7a**: δ 4.53 (d), δ 4.66 (d); **H-2′**: **6**,**7c**,**7d**: δ 3.35 (s);**7a**: δ 3.30 (s); **7b**: δ 3.25 (s); **H-4′**, **H-5′**: **9**,**10**,**11**: δ 3.55 (m, 4H); **H-15**: **11**: δ 1.06 (s, 3H); multiplicities are not repeated if identical with those in the preceding column.

[a] Recorded in C_6D_6.

Table 4
^{13}C NMR chemical shifts (50.3 MHz, signal of residual solvent centred at δ 77.0 ppm for CH_3Cl and δ 128.0 ppm for C_6H_6)[a]

C	5	6	7a	7b	7c	7d	8	9[b]	10[b]	11[b]	12	13
1	44.5 d	44.6	21.8 t	21.3	21.4	21.6	21.3	21.3	21.1	21.5	40.1 d	44.5
2	213.4 s	213.5	24.4 t	24.5	22.4	22.7	22.3	22.9	26.0	35.5	73.9 d	212.7 s
3	37.3 t	37.3	27.4	27.3	27.5	27.3	30.1	30.6	37.3	39.7 d	26.1 t	37.1
4	39.9 t	39.9	86.0 d	86.2	86.4	86.4	80.9	80.7	212.7 s	213.9	38.7 t	39.6
4a	36.5 s	36.6	39.5	39.2	39.5	39.3	39.5	39.3	48.6	48.6	36.4	37.7
4b	54.4 d	54.9	—	—	—	—	—	—	—	—	56.3 d	55.2
5	20.4 t	20.6	37.5	37.5	38.3	37.5	37.9	32.7	32.7	32.7	24.0	21.5
6	24.3 t	24.4	20.6	24.8	24.6	24.8	24.6	25.0	22.0	22.1	24.4	26.0
6a	—	—	47.7 d	49.2	56.0	49.1	55.9	52.4	52.0	52.0	—	—
7	30.0 t	27.4	160.3 s	53.8 d	31.1	51.3	31.0	28.4	28.3	28.3	30.1 t	37.4
8	80.7 d	86.3	129.2 d	208.8 s	52.9 t	217.1 s	52.9 t	49.5	49.3	49.4	81.1 d	215.0 s
8a	39.2 s	39.2	—	—	—	—	—	—	—	—	40.6 s	48.6
9	37.9 t	38.3	206.2 s	128.5 d	214.9 s	40.8 7	214.9 s	111.9	111.7	111.7	38.8 t	33.2
10	21.7 t	21.8	39.2 t	141.1 d	39.3 t	20.9	39.3	38.8	34.5	34.6	19.9 t	20.5
10a	53.2 d	53.3	—	—	—	—	—	—	—	—	49.1 d	52.6
11	12.8 q	53.3	33.6 t	47.4	36.1	43.7	36.2	35.6	35.5	35.5	16.7	19.4
11a	—	—	38.7 s	39.9	39.8	40.1	39.7	39.7	40.4	40.5	—	—
11b	—	—	49.0 d	54.9	53.9	54.2	53.5	53.4	53.6	54.5	—	—
12	11.5 q	13.9	14.4	13.1	14.1	13.4	13.1	13.4	19.6	19.8	8.6	11.5
13	13.6 q	11.5	22.7	19.5	22.1	17.3	22.0	21.1	21.1	21.1	12.9	13.9
14	—	—	20.1 q	14.5	13.9	13.6	14.0	16.4	16.6	16.5	—	—

C-1′:**6**,**7a**: δ 95.5 (t); **7b**,**7c**,**7d**: δ 95.6 (t); **C-2′**: **6**,**7c**: δ 55.4 (q); **7a**,**7b**, **7d**: δ 55.5 (q); **C-4′**, **C-5′**: **9**,**10**,**11**: δ 63.8, δ 64.2; **C-15**: **11**: δ 15.5.
[a] Degree of protonation and assignments were established by gHSQC experiments; multiplicities are not repeated if identical with those in the preceding column.
[b] Recorded in C_6D_6.

adding an excess of acetic anhydride. The reaction was allowed to complete after 12 h at room temperature and then quenched by adding distilled water, extracted with AcOEt (3×) and the combined organic layers washed several times with a aqueous solution of $CuSO_4$ (satd) until the pyridine was removed. The remaining organic layer was then dried over anhydrous $NaSO_4$, filtered, and concentrated in vacuum. The acetylated derivatives were obtained in a quantitative yield.

4.5. Methoxy-methyl (MOM) derivatives were prepared as follows

A solution of compound **5** (225 mg, 1.14 mmol) in 10 mL of dry dichloromethane (DCM) was cooled at 0 °C and then 292 μL of DiPEA (1.7 mmol) and 140 μL of MOMCl (1.7 mmol) were added. The reaction mixture was kept under reflux for 20 h. The reaction was quenched by adding a saturated aqueous solution of NH_4Cl. The organic layer was separated and the aqueous phase partitioned using AcOEt (3×). The combined organic phases were washed using aqueous HCl (1 N), dried over anhydrous $NaSO_4$, filtered, and concentrated in vacuum. The MOM ether **6** was obtained in a 90% yield.

*4.5.1. (1S,4aS,4bR,8R,8aR,10aS)-8-Methoxymethoxy-1,4a,8a-trimethyldodecahydrophenanthren-2(1H)-one (**6**).* $C_{19}H_{32}O_3$; colourless oil; $[\alpha]_D^{20}$ +20 (*c* 0.06, MeOH); IR $\nu_{max}^{neat,\ KBr}$ cm^{-1}: 1710 (ν C=O); HRMS calcd for $C_{19}H_{32}O_3$ 308.2351, found 308.2354; EIMS (70 eV) *m*/*z* (rel int.): 308 $[M]^+$ (51), 276 $[M-CH_3OH]^+$ (100), 263 $[M-C_2H_5O]^+$ (48), 109 (47), 81 (65), 55 (81). ^1H NMR (400 MHz, $CDCl_3$): see Table 3 *J*(Hz): H-1 (5.7); H-3 (0.9, 6.9, 13.2); H-3′ (2.3, 5.6, 13.2); H-4 (2.3, 6.8, 13.2); H-4b (2.6, 11.8); H-5 (3.8, 12.7); H-7′ (4.3, 13.0, 13.0); H-8 (4.0, 11.5); H-9 (3.2, 3.2, 13.0), H-9′ (3.8, 13.3, 13.3); H-10 (3.4, 17.7); H-10a (3.1, 3.1, 12.4); H-12 (6.5); H-1′a (6.9); H-1′b (6.9). ^{13}C NMR (50.3 MHz, $CDCl_3$): see Table 4.

4.6. General procedure for homologation

Conditions (d) (according to the key in Fig. 3): 600 μL (1.25 mmol) of a Me_3Al solution (2 M) in hexanes were added to 20 mL of dry DCM at −78 °C. Then the starting material (0.5 mmol) dissolved in 5 mL of dry DCM were added, followed by 600 μL (1.25 mmol) of a $TMSCHN_2$ solution (2 M) in hexanes. The reaction was stirred and allowed to reach room temperature for 12 h. After this period the reaction mixture was diluted with 25 mL of *n*-pentane and cooled again at 0 °C before adding 5 mL of aqueous $NaHCO_3$ (2.5%). The two phase system were slowly stirred for 5 min and immediately washed with cooled aqueous HCl (0.05 N), aqueous $NaHCO_3$ (2.5%), and brine. The organic layer was then dried over anhydrous Na_sSO_4, filtered, and the solvent evaporated in vacuum at 0 °C.

Dehydrosylilation was carried out without any purification using the reaction crude obtained from the homologation step. The crude of reaction was dissolved in acetonitrile (ACN, 10 mL) and then benzoquinone (BQ, 0.25 mmol) and $Pd(OAc)_2$ (0.25 mmol) were added. The reaction mixture was stirred at room temperature for 24 h and quenched by adding distilled water. The ACN was evaporated in vacuum and the resulting aqueous phase partitioned with EtOAc (3×). The combined organic layers were dried over anhydrous Na_sSO_4, filtered, and the solvent evaporated in vacuum to yield the mixture of regioisomeric unsaturated cycloheptenones in a 57% overall yield (**7a** 22%, **7b** 35%) in the case of using compound **6** as starting material and the yields shown in Table 2 in the case of using the decalone **3** as starting material.

*4.6.1. (4R,4aR,6aS,7S,11aS,11bR)-4-(Methoxymethoxy)-4a,7,11a-trimethyl-1,2,3,4,4a,5,6,6a,10,11,11a,11b-dodecahydro-9H-cyclohepta[a]naphthalen-9-one (**7a**).* $C_{20}H_{32}O_3$; colourless oil; $[\alpha]_D^{20}$ +24 (*c* 0.1, MeOH); IR $\nu_{max}^{neat,\ KBr}$ cm^{-1}: 1654 (ν α,β-unsaturated C=O); HRMS calcd for $C_{20}H_{32}O_3$ 320.2351, found 320.2367; EIMS (70 eV) *m*/*z* (rel int.): 320 $[M]^+$ (100), 288 $[M-CH_3OH]^+$ (65), 258 $[M-OMOM]^+$ (68), 203 (45), 135 (68), 81 (59). ^1H NMR (400 MHz, $CDCl_3$): see Table 3 *J*(Hz): H-4 (4.3, 11.5); H-5 (3.6, 13.3, 13.3); H-5′ (3.3, 6.1, 13.3); H-6a (11.3); H-10 (2.0, 5.5, 18.4); H-10′ (1.5, 13.8, 18.2); H-11b (3.2); H-1′a (6.7); H-1′b (6.7). ^{13}C NMR (50.3 MHz, $CDCl_3$): see Table 4.

*4.6.2. (4R,4aR,6aS,7S,11aS,11bR)-4-(Methoxymethoxy)-4a,7,11a-trimethyl-1,2,3,4,4a,5,6,6a,7,11,11a,11b-dodecahydro-8H-cyclohepta[a]naphthalen-8-one (**7b**).* $C_{20}H_{32}O_3$; colourless oil; $[\alpha]_D^{20}$ +55 (*c* 0.1, MeOH); IR $\nu_{max}^{neat,\ KBr}$ cm^{-1}: 1660 (ν α,β-unsaturated C=O); HRMS calcd for $C_{20}H_{32}O_3$ 320.2351, found 320.2359; EIMS (70 eV) *m*/*z* (rel int.): 320 $[M]^+$ (100), 275 $[M-CH_3OCH_2]^+$ (52), 201 (66), 191 (85), 149 (95), 121 (77), 81 (59), 55 (70). ^1H NMR (400 MHz, $CDCl_3$): see Table 3 *J*(Hz): H-4 (4.1, 11.5); H-5α (3.2, 13.6, 13.6); H-7

(7.2, 7.2); H-9 (1.2, 2.6, 12.2); H-10 (4.1, 5.6, 12.2); H-11α (19.4); H-11β (1.0, 5.9, 19.4); H-13 (7.2); H-1′a (6.9); H-1′b (6.9). ^{13}C NMR (50.3 MHz, $CDCl_3$): see Table 4.

Conditions (e) (according to the key in Fig. 3): the two steps of the reaction (homologation and desylilation) were carried out as described for condition (d) excepting that the reactions were run under dark conditions. Purification by using HPLC (Hx/AcOEt) yielded the cycloheptanones **7c** (42%) and **7d** (15%).

*4.6.3. (4R,4aR,6aS,7R,11aS,11bR)-4-(Methoxymethoxy)-4a,7,11a-trimethyl-tetradecahydro-9H-cyclohepta[a]naphthalen-9-one (**7c**).* $C_{20}H_{34}O_3$; colourless oil; $[\alpha]_D^{20}$ +17 (*c* 0.1, MeOH); IR $\nu_{max}^{neat,\ KBr}$ cm^{-1}: 1700 (ν C=O); HRMS calcd for $C_{20}H_{34}O_3$ 322.2507, found 322.2539; EIMS (70 eV) *m/z* (rel int.): 322 [M]$^+$ (100), 250 (12), 181 (4), 125 (3), 100 (4). ^{1}H NMR (400 MHz, $CDCl_3$): see Table 3 *J*(Hz): H-2α (3.6, 13.8); H-4 (4.3, 11.5); H-5β (3.5, 3.5, 13.3); H-8α (13.3); H-8β (3.1, 13.3); H-10α (4.1, 5.1, 16.6); H-10β (16.9); H-11b (2.1, 11.2); H-13 (6.9); H-1′a (6.9); H-1′b (6.9). ^{13}C NMR (50.3 MHz, $CDCl_3$): see Table 4.

*4.6.4. (4R,4aR,6aS,7S,11aS,11bR)-4-(Methoxymethoxy)-4a,7,11a-trimethyl-tetradecahydro-8H-cyclohepta[a]naphthalen-8-one (**7d**).* $C_{20}H_{34}O_3$; colourless oil; $[\alpha]_D^{20}$ +56 (*c* 0.1, MeOH); IR $\nu_{max}^{neat,\ KBr}$ cm^{-1}: 1694 (ν C=O); HRMS calcd for $C_{20}H_{34}O_3$ 322.2507, found 322.2490; EIMS (70 eV) *m/z* (rel int.): 322 [M]$^+$ (100), 250 (11), 236 (4); 169 (1), 119 (5), 100 (2). ^{1}H NMR (400 MHz, $CDCl_3$): see Table 3 *J*(Hz): H-4 (4.4, 11.8); H-5β (3.3, 3.3, 13.3); H-7 (6.6); H-9α (3.6, 12.6, 12.6); H-11b (6.9); H-13 (6.9); H-1′a (6.7); H-1′b (6.7). ^{13}C NMR (50.3 MHz, $CDCl_3$): see Table 4.

Conditions (f) (according to the key in Fig. 3): both steps were run as for conditions (d) (homologation and dehydrosylilation) in a modified Hanovia photochemical reactor using as filter an aqueous solution of $CoSO_4$ (40%)/$NiSO_4$ (60%) under a UV Hg lamp (125 W). Purification by using HPLC (Hx/AcOEt) yielded compounds 7**a** (4%), 7**b** (16%), **7c** (13%), and **7d** (16%).

4.7. MOM deprotection

Compound **7c** (300 mg, 0.93 mmol) was dissolved in 5 mL of dry DCM containing molecular sieves (4 Å) in a Dewar vessel stabilized at 0 °C. Then, 490 μL of TMSBr were added and the solution stirred for 1 h. The reaction was monitored by TLC until all the starting material disappeared. Work-up: the reaction was stopped by adding a saturated aqueous solution of $NaHCO_3$ and the resulting mixture extracted with EtOAc (3×). The combined organic phases were dried over anhydrous Na_2SO_4 and the solvent evapd. in vacuum. The free hydroxylated compound **8** was obtained after purification by HPLC in a 81% yield.

*4.7.1. (4R,4aR,6aS,7R,11aS,11bR)-4-Hydroxy-4a,7,11a-trimethyltetradecahydro-9H-cyclohepta[a]naphthalen-9-one (**8**).* $C_{18}H_{30}O_2$; colourless oil; $[\alpha]_D^{20}$ +8 (*c* 1.0, MeOH); IR $\nu_{max}^{neat,\ KBr}$ cm^{-1}: 3339 (ν O–H), 1700 (ν C=O); HRMS calcd for $C_{18}H_{30}O_2$ 278.2245, found 278.2260; EIMS (70 eV) *m/z* (rel int.): 278 [M]$^+$ (8), 250 (100), 236 (4), 169 (1), 119 (5), 100 (2). ^{1}H NMR (400 MHz, $CDCl_3$): see Table 3 *J*(Hz): H-4 (4.4, 11.5); H-5α (3.3, 12.6, 12.6); H-5β (3.1, 3.1, 12.6); H-8α (13.3); H-8β (3.0, 13.3); H-10α (3.9, 5.1, 16.6); H-10β (3.0, 12.8, 17.2); H-11α (3.8, 12.8, 15.1); H-11β (4.6, 4.6, 15.1); H-11b (2.3); H-13 (6.9). ^{13}C NMR (50.3 MHz, $CDCl_3$): see Table 4.

4.8. Dioxolane derivative from 8

A mixture of 100 mg (0.35 mmol) of **8**, 2 mL of methyl ethyl dioxolane (MED, Sigma Aldrich, Co.), 100 μL of ethylene glycol, and a catalytic amount of *p*-toluenesulphonic acid were stirred at room temperature for 3 h. The complete conversion of the starting material was monitored by TLC. Work-up: 100 μL of triethylamine were added to the reaction and the reaction stirred for ten minutes. The crude was partitioned using EtOAc (3×) and the combined organic phases were dried over anhydrous Na_2SO_4, filtered, and evapd. in vacuum. The crude of reaction was separated by column chromatography (Hx/EtOAc 4:1) to yield **9** (80%).

*4.8.1. (4R,4aR,6aS,7R,11aS,11bR)-4a,7,11a-Trimethyltetradecahydrospiro[cyclohepta[a]naphthalene-9,2′-[1′,3′]dioxolan]-4-ol (**9**).* $C_{20}H_{34}O_3$; colourless oil; $[\alpha]_D^{20}$ −15 (*c* 0.1, MeOH); IR $\nu_{max}^{neat,\ KBr}$ cm^{-1}: 3348 (ν O–H); HRMS calcd for $C_{20}H_{34}O_3$ 322.2507, found 322.2511; EIMS (70 eV) *m/z* (rel int.): 322 [M]$^+$ (4), 279 (5), 207 (4), 153 (10), 113 (100), 99 (67). ^{1}H NMR (400 MHz, C_6D_6): see Table 3 *J*(Hz): H-3β (4.6, 11.8, 12.8, 12.8); H-4 (4.8, 11.8); H-8α (9.2, 11.8); H-8β (11.3); H-10α (3.1, 9.7, 14.6); H-11α (3.6, 7.2); H-11β (3.1); H-11b (2.3, 11.5); H-13 (6.7). ^{13}C NMR (50.3 MHz, C_6D_6): see Table 4.

4.9. Oxidation of 9

Pyridinium dichlorochromate (165 mg, 0.44 mmol, PDC, Sigma Aldrich, Co.) were added to a solution of **9** (80 mg, 0.25 mmol) in 20 mL of dry DCM under argon atmosphere. The reaction was allowed to proceed for 12 h until the complete transformation of the starting material. Work-up: the reaction mixture was filtered through Celite to remove the oxidant, the Celite washed with EtOAc and the solvent evapd. in vacuum. The reaction mixture was purified by column chromatography (Hx/AcOEt 7:3) to yield **10** (85%).

*4.9.1. (4aR,6aS,7R,11aS,11bR)-4a,7,11a-Trimethyldodecahydrospiro-[cyclohepta[a]naphthalene-9,2′-[1′,3′]dioxolan]-4(1H)-one (**10**).* $C_{20}H_{32}O_3$; colourless oil; $[\alpha]_D^{20}$ −21 (*c* 0.1, MeOH); IR $\nu_{max}^{neat,\ KBr}$ cm^{-1}: 1669 (ν C=O); HRMS calcd for $C_{20}H_{34}O_3$ 320.2351, found 320.2342; EIMS (70 eV) *m/z* (rel int.): 320 [M]$^+$ (4), 277 (4), 249 (4), 181 (6), 153 (3), 140 (12), 113 (100), 99 (88). ^{1}H NMR (400 MHz, C_6D_6): see Table 3 *J*(Hz): H-1α (3.8, 12.8, 12.8); H-3α (1.3, 2.1, 5.1, 14.1); H-3β (6.9, 13.1, 14.1); H-8α (11.0); H-8β (12.6); H-11α (3.1, 7.9, 14.6); H-11β (3.8, 9.5, 14.9); H-11b (2.3, 11.5); H-13 (6.7). ^{13}C NMR (50.3 MHz, C_6D_6): see Table 4.

4.10. Alkylation of 10

Potassium tert-butoxide (0.18 mmol, 180 μL of a 1 M solution in THF) was added to a solution of **10** (60 mg, 0.18 mmol) in dry THF at −10 °C under argon atmosphere and stirred for 1 h to generate the enolate. The enolate was then allowed to react with MeI (40 μL, 0.62 mmol) and the temperature rose from −10 °C to room temperature. After three hours of stirring the reaction was completed. Work-up: a saturated aqueous solution of NH_4Cl was added to the reaction mixture, partitioned with EtOAc (3×) and the combined organic phases dried over anhydrous Na_2SO_4, filtered, and evapd. in vacuum. The reaction mixture was purified by HPLC (Hx/AcOEt 4:1) to yield **11** in a 90%.

*4.10.1. (3S,4aR,6aS,7R,11aS,11bR)-3,4a,7,11a-tetramethyldodecahydrospiro[cyclohepta[a]naphthalene-9,2′-[1′,3′]dioxolan]-4(1H)-one (**11**).* $C_{21}H_{34}O_3$; white crystals; mp=73–75 °C (uncorrected); $[\alpha]_D^{20}$ −21 (*c* 0.1, MeOH); IR $\nu_{max}^{neat,\ KBr}$ cm^{-1}: 1669 (ν C=O); HRMS calcd for $C_{21}H_{34}O_3$ 334.2507, found 334.2512; ^{1}H NMR (400 MHz, C_6D_6): see Table 3 *J*(Hz): H-1β (3.7, 12.4, 13.1); H-2α (4.4, 13.1, 13.1, 13.1); H-3β (6.2, 6.2, 12.4); H-11α (3.3, 10.2, 14.6); H-11β (2.3, 7.7, 14.8); H-11b (2.6, 12.3); H-15 (6.4). ^{13}C NMR (50.3 MHz, C_6D_6): see Table 4. X-ray analysis: complete tables of distances, angles, torsion angles, least-square planes, anisotropic thermal parameters, and structure factors have been deposited with the Cambridge Crystallographic Data

Centre (Deposition number CCDC 736286). Copies may be obtained through the Executive Secretary.

4.11. Molecular modelling

Minimum energy conformers and heats of formation were obtained using semi-empirical calculations (PM3, Spartan'08). Spatial geometry was optimized using the keywords precise and geo-OK. Results are shown in the Supplementary data file.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2010.03.116. These data include MOL files and InChIKeys of the most important compounds described in this article.

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