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A synthetic approach to (±)-forskolin. Part II. Radical approaches of the AB ring system and formal synthesis of (±)-forskolin

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Summary — A 6-endo-trig cyclization was performed from enynes **8** and **10** using Bu_3SnH/AIBN, leading to the construction of the *trans*-decalinic AB ring system of (±)-forskolin **1**. In a second radical approach to (±)-forskolin **1**, the diol **31** was oxidized to dialdehyde **6**. A pinacolic coupling reaction promoted by SmI_2 then delivered the cyclized 6β,7β-diol **41**. From this compound the unsaturated lactone **2** was then prepared leading to a formal synthesis of (±)-forskolin **1**.

forskolin / formal synthesis / tributylstannane / radical cyclization / 6-endo-trig process / samarium iodide / pinacolic coupling reaction / Dess–Martin oxidation

Résumé — Approche de synthèse de la (±)-forskoline. Partie II: approches radicalaires du système bicyclique AB et synthèse formelle de la (±)-forskoline. À partir des énynes **8** et **10** une cyclisation de type 6-endo-trig a été réalisée par action de Bu_3SnH/AIBN, conduisant à la préparation du système AB *trans* décalinique de la (±)-forskoline **1**. Dans une seconde approche de la (±)-forskoline **1**, le diol **31** a été oxydé en dialdéhyde **6**. Un couplage pinacolique a ensuite été obtenu par traitement du dialdéhyde **6** avec SmI_2 et a conduit au dérivé 6β,7β-diol **41**. À partir de ce dernier, la lactone insaturée **2** a pu être préparée, nous permettant ainsi de réaliser une synthèse formelle de la (±)-forskoline **1**.

forskoline / synthèse formelle / tributylstannane / cyclisation radicalaire / 6-endo-trig cyclisation / samarium iodure / couplage pinacolique / oxydation Dess–Martin

In our program towards the total synthesis of forskolin **1** [1], we focused on the preparation of the unsaturated lactone **2** which was used, as a pivotal synthon, by Corey, Ikegami and Ziegler for the total synthesis of forskolin **1** [2]. As described in a preceding paper [3], we decided to develop two radical cyclizations for the preparation of the bicyclic core of forskolin **1**. In a preliminary approach, a C7-C8 closure, leading to compound **3**, was envisaged from the enyne **4** (scheme 1) [4]. A second radical cyclisation induced by SmI_2 on the dialdehyde **6** must give the bicyclic diol **5** via a pinacolic coupling reaction [5]. In this paper we describe the two synthetic approaches developed in our laboratory and the synthesis of the lactone (±)-**2** as a formal synthesis of racemic forskolin (±)-**1** [6].

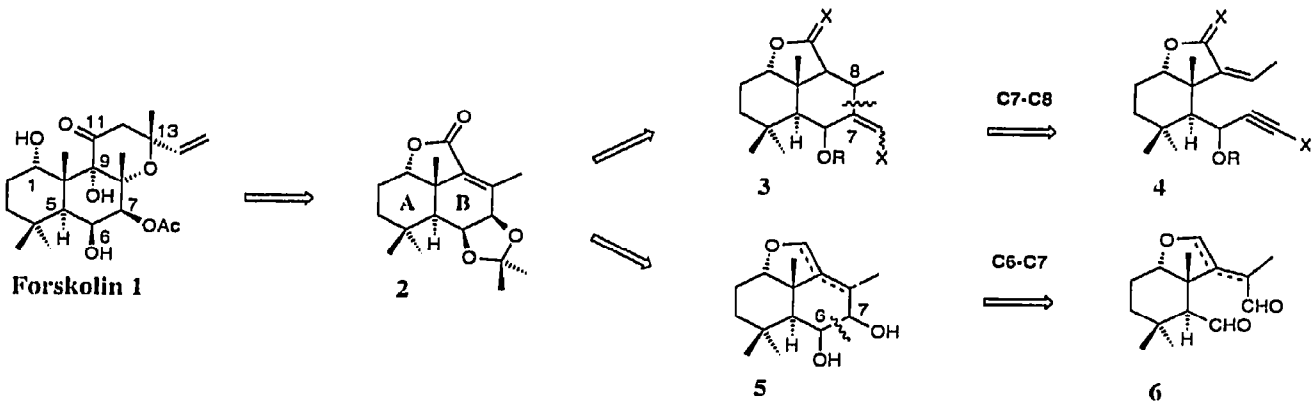
Preparation of the AB ring system via a C7-C8 bond closure

In a preceding paper [3] we described the preparation of the hydrobenzofuran enyne derivatives **8–10** via a preliminary radical cyclisation via a 6-endo-trig process.

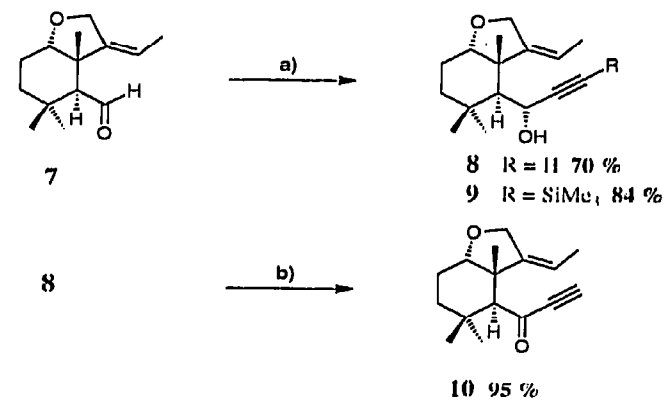
To perform a radical cyclization induced by Bu_3SnH [7] from the enyne compounds **8–10** it was necessary to run the reaction under dilute conditions to favor the 6-endo-trig cyclization. Using a 10^{-2} solution of the enynol **8** in boiling toluene, the reaction was performed by a slow addition (6 h) of Bu_3SnH/AIBN. In this case the expected bicyclic derivative **11** was obtained as the only isomer in 46% yield (scheme 2). The structure of **11** was elucidated with the aid of ^1H NMR analysis and NOE experiments. In this reaction, addition of the $Bu_3Sn^{\cdot}$ radical on the triple bond led to the vinylic radical **I** which cyclized on the double bond (scheme 3). Intermediate **II** was trapped by a $H^{\cdot}$ capture and the cyclized compound **III** was obtained. From **III** a protodestannylation reaction occurred, probably due to the acidic proton of the proximal hydroxyl function, and afforded the decalinic derivative **13**. Stereoselective addition of $H^{\cdot}$ on the intermediate **II** on the β side was interpreted to be a consequence of the bent structure of **II**.

Starting from the silyl derivative **9** we also tried to perform the desired 6-endo-trig cyclization under the same conditions as used before. Protection of the acetylenic function with the TMS group had a dramatic

* Correspondence and reprints

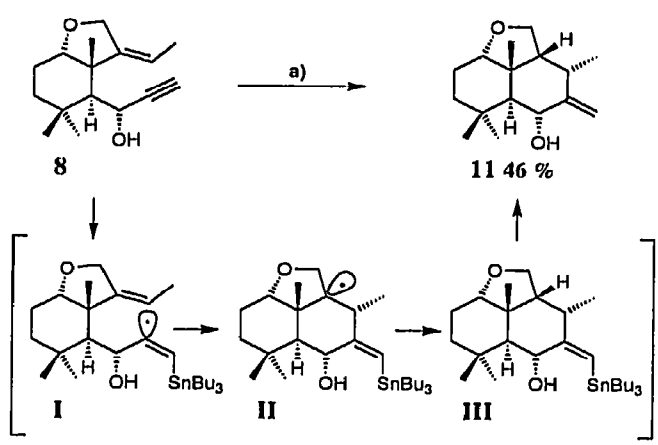


Scheme 1



a) and b) see ref 3.

Scheme 2

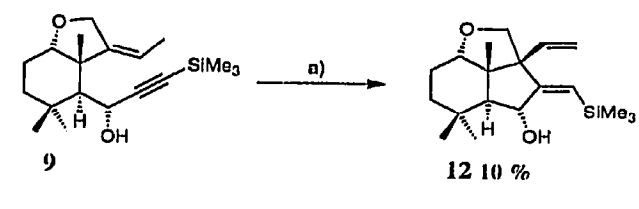


a) Bu_3SnH (1 equiv), AIBN (10 mol%), toluene, Δ, 6 h, 46%.

Scheme 3

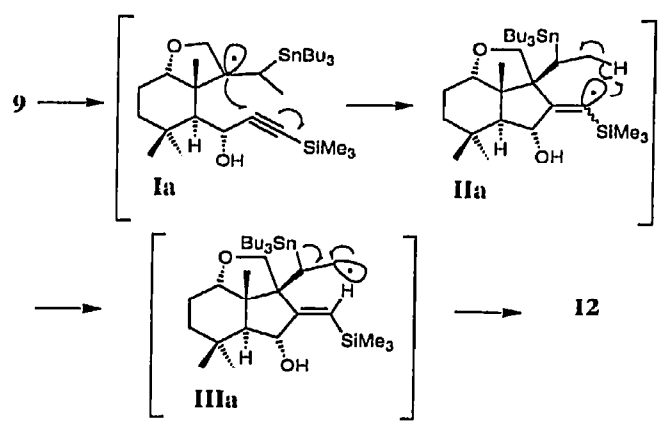
effect on the cyclization reaction. The reaction occurred in only 10% yield and the only isolated product was the unexpected tricyclic derivative **12** (scheme 4).

For an explanation of this reaction we had to involve a $Bu_3Sn^{\bullet}$ addition on the double bond rather than on



a) Bu_3SnH (1 equiv), AIBN (10 mol%), toluene, Δ, 6 h, 10%.

Scheme 4



Scheme 5

the silylated triple bond (scheme 5). This chemioselectivity could be due to the steric hindrance at this position which has been previously observed [3]. From the radical intermediate **Ia**, generated in the first step, a 5-exo-dig radical process could deliver the vinylic radical species **IIa**. From **IIa** a 1,5-hydrogen transfer was envisaged which led to intermediate **IIIa**, the loss of Bu_3SnH in the last step then delivered the tricyclic compound **12** [8]. This reaction mechanism accounted for the formation of the pure *Z* vinylsilane isomer.

Formation of **12** via an ene-reaction can be excluded since heating **9** without addition of Bu_3SnH did not deliver a cyclized product. In order to prove the catalytic importance of Bu_3SnH in this mechanism, compound **9** was treated with 10 mol% of Bu_3SnH but cyclization occurred in only 5% yield and the reaction mechanism

could not be proved at this time due to the poor yield of this reaction.

When the ynone **10** was treated with Bu_3SnH under the same conditions as for compound **8**, the stannyl derivative **13** was prepared in 55% yield (scheme 6). In this case, protodestannylation did not occur and the vinylstannyl **13** was obtained as the pure *Z* isomer.

The results we obtained for our strategy for the construction of the AB ring system of (±)-forskolin **1** using a radical key step cyclization, were promising and the final experiment involved testing this cyclization on the enone-ynone derivative **4a** envisaged before.

Unfortunately, starting with compound **10**, oxidation with SeO_2 using Sharpless or Salmond conditions [9] did not lead to the expected lactone **4a** or the corresponding lactol or hemiacetal (scheme 6).

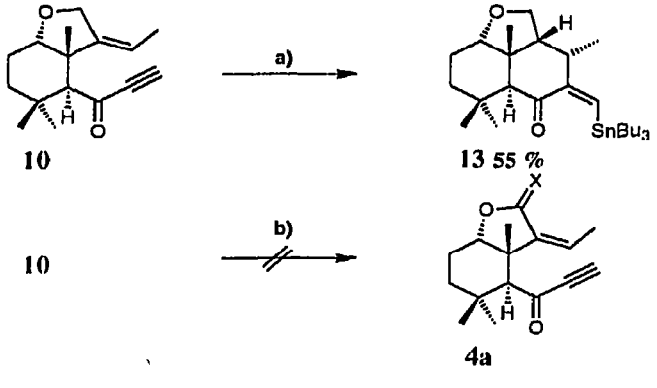
Because the ethylidene group was not a suitable group for the Sharpless oxidation we decided to prepare the lactone derivative **18** (scheme 7). Starting from **14a** [3] we were able to prepare the 5α-H aldehyde **15** and then the ynone **16** as described for the preparation of **10**. At this stage oxidation of **16** using SeO_2 did not lead to lactone **18** and the hemiacetal **17** was obtained in 13% maximum yield (scheme 7).

These disappointing results prompted us to use the Sharpless oxidation on the methylene compound **14b** and the lactone **19** was produced in 67% yield. To continue the synthesis the acetal **20** was also prepared from **19** in 75% yield (scheme 7).

Having resolved the problem of oxidation in the α-position of the methylene function we focused on the preparation of the enyne-dione **18** from **17** or **20** (scheme 8). Application of the radical cyclization used above, must deliver the expected tricyclic product **21**, which was a possible precursor of the key lactone **2**.

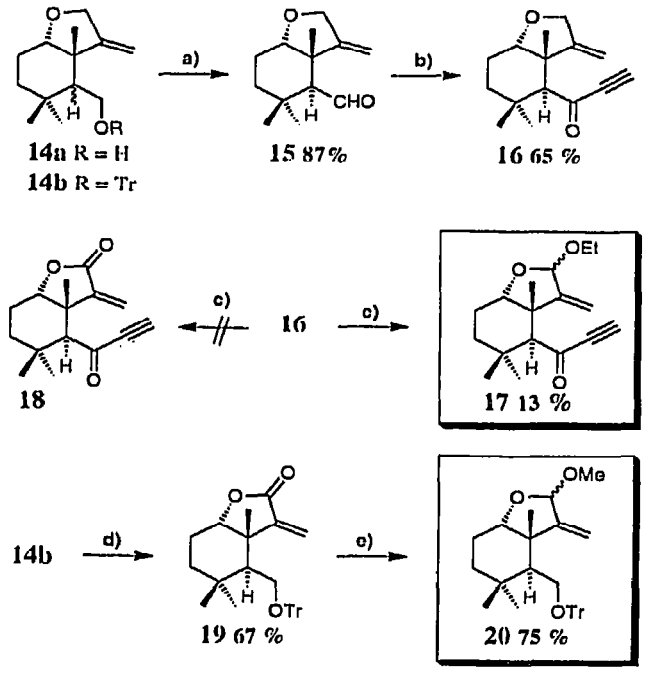
Preparation of the AB ring system via a C6-C7 bond closure

In a second radical cyclization approach (see scheme 1), our initial project was to form the B ring of (±)-forskolin **1** using a pinacolic reaction, promoted by SmI_2, from the dialdehyde **6** (see scheme 1) or the nitrile-aldehyde **23** [10]. This route must deliver a



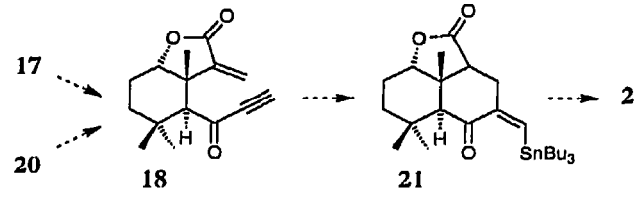
a) Bu_3SnH (1 equiv), AIBN (10% mol), toluene, Δ, 6 h, 55%. b) SeO_2, H_2O, dioxane, Δ.

Scheme 6



a) (i) PCC, CH_2Cl_2, 20 °C, 1.5 h, 95%. (ii) K_2CO_3, MeOH, Δ, 3 h, 92%. b) (i) C≡CLi·TMEDA, THF, 20 °C, 12 h, 75% (ii) Dess–Martin, CH_2Cl_2, 20 °C, 1 h, 86%. c) (i) SeO_2, H_2O, dioxane, Δ, 5 h. (ii) Amberlist $15H^+$ EtOH, 20 °C, 2 h, 13%. d) SeO_2, H_2O, dioxane, Δ, 5 h, 67%. e) (i) DIBALH, toluene, −78 °C, 1 h. (ii) Amberlist $15H^+$, MeOH, 20 °C, 2 h, 75%.

Scheme 7

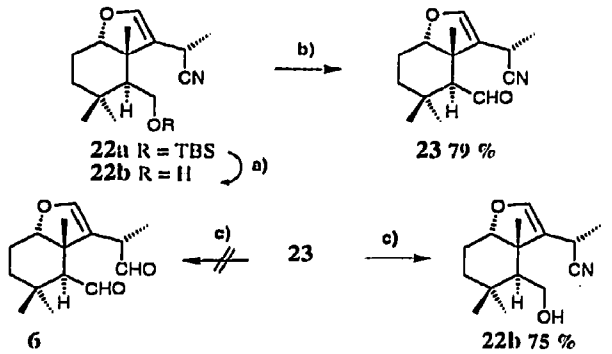


Scheme 8

highly substituted AB ring system with two oxygenated functions at C6 and C7.

Starting from the nitrile-ether derivative **22a** described in our preceding paper [3], desilylation provided the nitrile-alcohol **22b** (scheme 9). This compound underwent an oxidation reaction using the Dess–Martin reagent to give the expected nitrile-aldehyde **23** in 79% yield. In order to prepare the dialdehyde **6**, the nitrile-aldehyde **23** was treated with diisobutylaluminium hydride (DIBALH) but reduction of aldehyde occurred faster than reduction of the nitrile function and the nitrile-alcohol **22b** was obtained in 75% yield (scheme 9).

For the preparation of the dialdehyde **6** we also envisaged an oxidation of the corresponding diol derivative **31** (scheme 10) which was obtained from the conjugated ester **24** [3]. We then performed a one-pot reaction of the deconjugation of the unsaturated system. A stereospecific alkylation of the resulting ester **28** then led to the expected diol **31** either after reduction into **30**



a) HF, acetonitrile, 20 °C, 1 h, 90%. b) Dess–Martin, CH_2Cl_2, 20 °C, 79%. c) DIBALH, toluene, −78 °C, 1 h, → **22b** 75%.

Scheme 9

and deprotection of the primary alcohol, or by reduction of lactone **29** which was obtained quantitatively from **28** by treatment with tetrabutylammonium fluoride (TBAF) in THF [3].

Once we had obtained the diol derivative **31**, we turned to an appropriate oxidation reaction to prepare the dialdehyde **6**.

We first tried to oxidize both of the primary alcohols under different conditions. The alcohol **30** gave the corresponding aldehyde **32** in 88% yield using Dess–Martin reagent (scheme 11) [11], whereas oxidation with the SO_3·pyridine complex in DMSO in the presence of NEt_3 [12] led to the cyclized compound **33b** in 73% yield. Oxidation using Swern conditions [13] gave a complex mixture.

After desilylation of **24**, the ester-alcohol **25** was oxidized into the aldehyde **26** in good yield (83%) using a Swern oxidation reaction.

As an interesting reaction, we wanted to perform a deconjugation reaction of the unsaturated ester function in the aldehyde **26**. Treatment of **26** in basic media [1,8-diazobicyclo[5.4.0]undec-7-ene (DBU), toluene, Δ] delivered the tricyclic compound **27** in 65% via an intramolecular Michael addition of the enol onto the conjugated ester (see scheme 10).

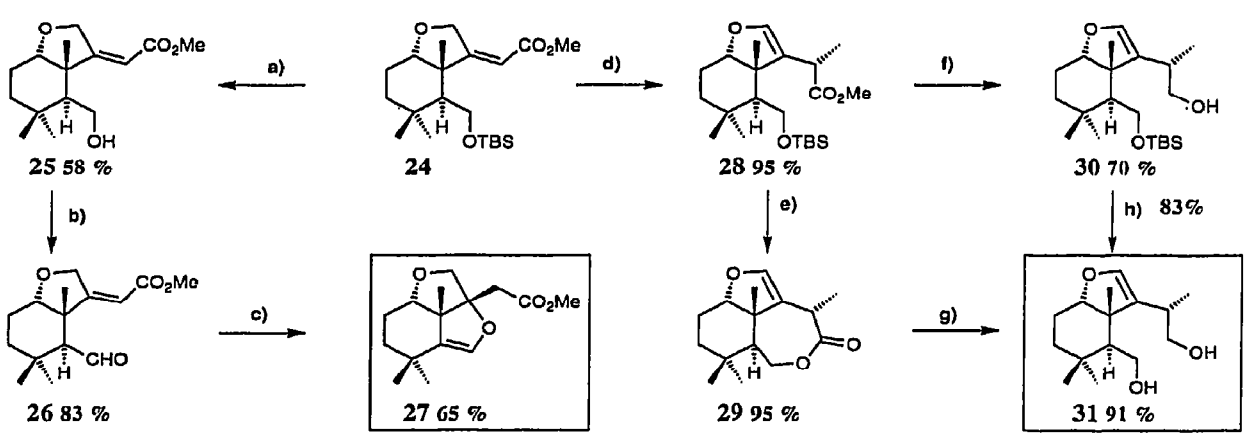
Starting from diol **31** we then applied different oxidation conditions, but aldehyde **6** could not be obtained using Swern conditions [12], pyridinium chlorochromate (PCC) [14], Dess–Martin [11], tetrapropylammonium perruthenate (TPAP) [15], or SO_3·pyridine complex [12] reagents. We also tried to oxidize the bis-silylated compound **34** using Swern conditions [16] but the only product, isolated in 73% yield, was the tricyclic compound **33a** (scheme 11). Compound **33a** was also obtained in 30% yield during the silylation of diol **31** into **34**.

At this stage we have shown that the two primary alcohol functions of diol **31** can be oxidized separately but the dialdehyde **6** was not obtained using classical oxidation reactions from diol **31** or bis-silylether **34**. Using the Dess–Martin reagent [11] (3 equiv) in CH_2Cl_2, reaction with **31** led to the two isomeric lactones **29** and **35** (scheme 12). However, the formation of the two lactones **29** and **35** involved the intermediate formation of lactols **36** and **37**, which could be considered as the cyclized forms of corresponding monoaldehydes. In order to attempt an oxidation into the dialdehyde **6** we had to minimize the intermediate formation of lactols **36** and **37**.

Looking at the mechanism involved for the Dess–Martin oxidation, it appears that during this reaction 2 equiv of acetic acid are produced. On the other hand, it has also been described that treatment of a diol derivative such as pinacol leads to a stable pinacolate complex under anhydrous conditions; oxidation could be achieved when *tert*-BuOH was added to the reaction mixture.

With this mechanistic information on the oxidation reaction with the Dess–Martin reagent we then tried different experiments either by addition of pyridine (entry 2), *tert*-BuOH (entry 3) or pyridine and *tert*-BuOH (entry 4). As reported in table I, aldehyde **6** could be obtained in 20% yield at best when 3 equiv of the Dess–Martin reagent were used in the presence of 6 equiv of pyridine and 3 equiv of *tert*-BuOH in CH_2Cl_2 at 20 °C (entry 4).

Because it was also described that the Dess–Martin reagent could be a better oxidant in the presence of 3 equiv of water [17], this reaction was also performed on the diol **31** but aldehyde **6** was not obtained (entry 5). Oxidation was also carried out using the iodoxybenzoic acid (IBX) reagent in DMSO [18] and aldehyde **6** was produced in 15% yield (entry 7). For the two

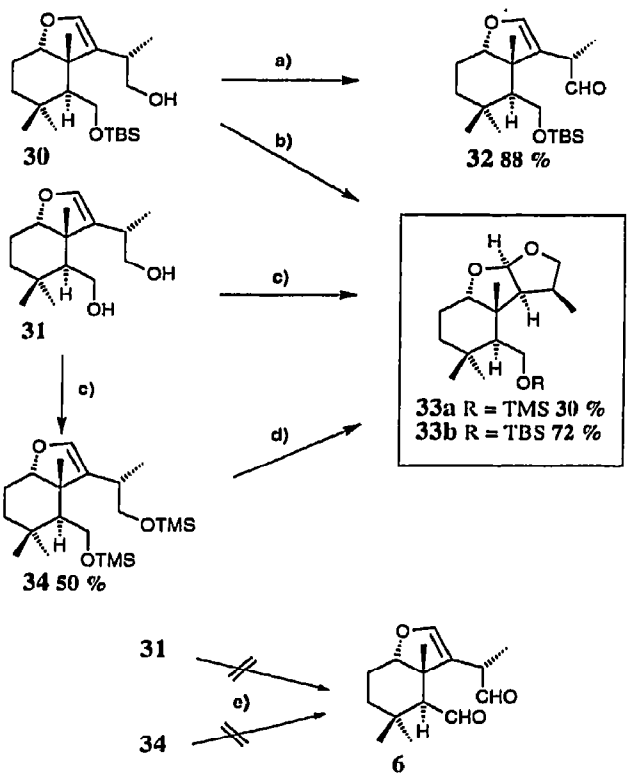


a) TBAF, THF, 20 °C, 12 h, 58%. b) Swern oxidation 83%. c) DBU, toluene, 65 °C, 4 h, 65%. d), e), f), g), h), see ref [3].

Scheme 10

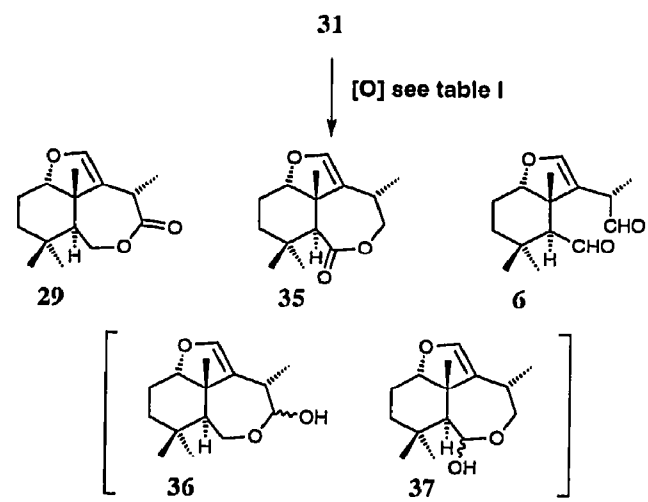
Table I. Oxidation of diol 31.

Entry	*Conditions*	*Yields 6, 35 and 29*
1	Dess–Martin (3 equiv), CH_2Cl_2, 20 °C	–, 69%, 20%
2	Dess–Martin (3 equiv), Py (6 equiv), CH_2Cl_2, 20 °C	10%, 64%, 13%
3	Dess–Martin (3 equiv), *tert*-BuOH (3 equiv), CH_2Cl_2, 20 °C	5%, 58%, 17%
4	Dess–Martin (3 equiv), Py (6 equiv), *tert*-BuOH (3 equiv), CH_2Cl_2, 20 °C	20%, 65%, 10%
5	Dess–Martin (3 equiv), H_2O (3 equiv), CH_2Cl_2, 20 °C	–, 56%, 25%
6	Dess–Martin (3 equiv), H_2O (3 equiv), Py (6 equiv), *tert*-BuOH (3 equiv), CH_2Cl_2, 20 °C	15%, 57%, 14%
7	IBX, DMSO, 20 °C	15%, 19%, 51%
8	TPAP (10 mol%), NMO (3 equiv), CH_3CN, 20 °C	10%, 35%, 47%
9	Grieco's reagent (3 equiv), Py/CH_2Cl_2/THF 1:1:1 excess, 20 °C	–, –, –



a) Dess–Martin, CH_2Cl_2, pyridine, 20 °C, 1.5 h, 88%. b) SO_3·pyridine, DMSO, NEt_3, 20 °C, 3 h, 72%. c) TMSCl, CH_2Cl_2, NEt_3, 20 °C, 12 h, → **33a** 30%, → **34** 50%. d) Swern oxidation, → **33a** 30%. e) PCC oxidation, SO_3·pyridine, DMSO, NEt_3, Swern oxidation.

Scheme 11



Scheme 12

last experiments, the TPAP [15] reagent led to the dialdehyde **6** in only 10% yield (entry 8) whereas the Grieco reagent [19] did not give the dialdehyde **6** or lactones **29** and **35**. The only compounds detectable in this reaction by ^1H NMR analysis were the two lactols **36** and **37** (entry 9).

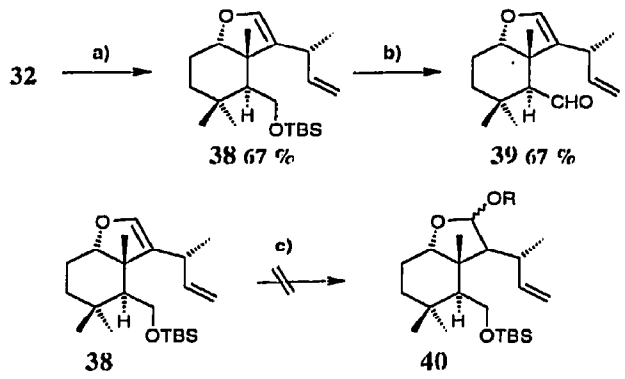
In most cases reported for the oxidation of diol **31**, lactone **35** was the major product of the reaction except when IBX was used (entry 7) where lactone **29** was obtained as the main product.

At this time we had no arguments for an explanation of this result. A more complete study of oxidation of diol **31** must be envisaged to increase the yield of dialdehyde **6**.

In order to prepare the dialdehyde **6** in better yield we needed to generate the second aldehyde function (at C6) via an ozonolysis reaction on a compound which already masks an aldehyde in the C5 position (scheme 13).

This route was explored using a Wittig reaction as the first step leading to **38** (67% yield) and an oxidation to afford the aldehyde **39** (67% yield). Because the ozonolysis reaction could not be used in the presence of the dihydrofuran function we decided to transform the dihydrofuran derivative **38** into the hemiketal **40** but all of the conditions we tried failed and compound **40** could not be prepared in acceptable yield.

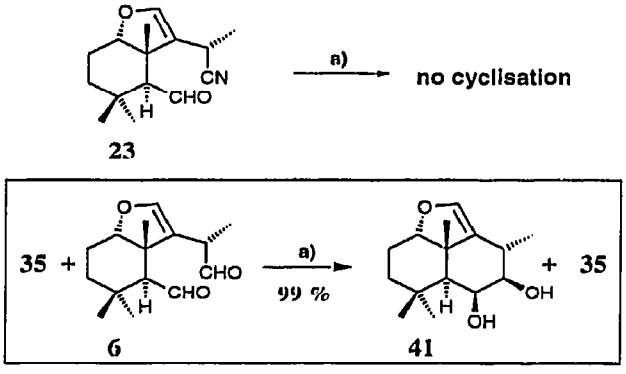
In spite of this disappointing result and the poor yield obtained during the synthesis of the dialdehyde **6**, we decided to pursue our synthetic approach and perform the pinacolic coupling reaction from the nitrile-aldehyde **23** and the dialdehyde **6**.



a) PPh_3CH_3Br, *n*-BuLi, THF, 20 °C, 12 h, 67%. b) (i) HF, acetonitrile, NEt_3, 20 °C, 1 h; (ii) Dess-Martin, CH_2Cl_2, 20 °C, 1.5 h, 67%. c) Amberlist $15H^+$, MeOH, 20 °C.

Scheme 13

Treatment of the nitrile-aldehyde **23** by SmI_2 in THF in the presence of *tert*-BuOH led to the reduced product **22b**, no cyclization occurred (scheme 14). It has been reported that nitrile is a weaker radical acceptor than aldehyde [10c].



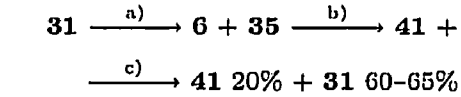
a) SmI_2, THF, *tert*-BuOH, −78 °C1 h, −78 °C → 20 °C, 2 h, >95%.

Scheme 14

When a 9:2 mixture of lactone **35** and aldehyde **6** (**35** and **6** were not separated by chromatography on silica gel) was treated with SmI_2 under the same conditions used for **23**, the expected cyclization occurred in 99% yield and the diol **41** was obtained as the 6β-7β isomer only, as proved by X-ray analysis [5]; the lactone **35** (**35**/**41** = 9:2) was quantitatively recovered. This remarkable stereoselectivity was in total agreement with the results obtained by Hanessian and coworkers in this field [20].

Because this cyclization reaction gave good yields we performed the three steps involving oxidation, SmI_2 treatment and reduction from the diol **31**. Three cycles of this reactional sequence delivered the cyclic diol **41** in 40% yield calculated from diol **31** (equation 1).

As depicted in scheme 1, the two radical approaches envisaged for the construction of the AB ring system of (±)-forskolin **1** were carried out: the second route



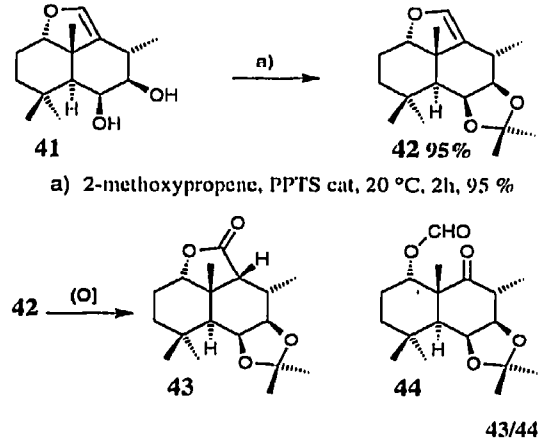
Three cycles → **41** in 40% yield. a) Dess-Martin, pyridine, *tert*-BuOH, CH_2Cl_2. b) SmI_2, THF, *tert*-BuOH, −78 °C, 1 h, −78 °C → 20 °C, 1 h. c) LAH, THF, 2 h, → **41** 20%, → **31** 60-65%.

Equation 1

using SmI_2 gave the suitable substituted 6β,7β diol **41** leading to access to the lactone synthon **2**.

Formal synthesis of (±)-forskolin 1

After construction of the cyclized diol **41** was achieved we then turned to the final steps for the preparation of unsaturated lactone **2**, the key intermediate for total synthesis of forskolin **1**. A protection of the diol **41** was first performed in acidic conditions to deliver the ketal derivative **42** in 95% yield (scheme 15). We then tried to oxidize the dihydrofuran derivative **42** into lactone **43**. As shown in scheme 15 direct oxidation of **42** with PCC led to a 1:1 mixture of the expected lactone **43** and the cleaved product formyl-ketone **44**. Compound **44** was quantitatively obtained by ozonolysis of **42**. Using the Dess-Martin reagent, oxidation of **42** resulted in a total cleavage of the dihydrofuran derivative **42** to furnish compound **44**.

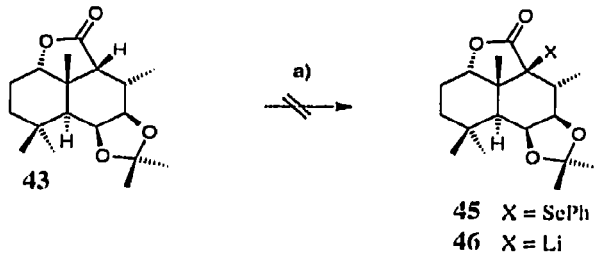


a) 2-methoxypropene, PPTS cat, 20 °C, 2h, 95 %

A) PCC (4.5 equiv), CH_2Cl_2, 20 °C, 3 h, 86%, 50:50; B) O_3, CH_2Cl_2, MeOH, −78 °C, Me_2S excess, −78 °C→ 20 °C, 17 h, 95% 0:100; C) MeOH, Amberlist 15 H^+, 20 °C, 17 h, 90%, 2-methoxypropene, PPTS cat, 20 °C, 2 h, 95%, *m*-CPBA (1.1 equiv), $BF_3{\cdot}OEt_2$ (0.1 equiv) CH_2Cl_2, 0 °C → 20 °C, 3 h, 80%, 68%, 100:0; D) Dess-Martin (1.5 equiv), CH_2Cl_2, 25 °C, 1 h, 92%, 0:100.

Scheme 15

The best method to prepare **43** in a pure form was an acidic treatment in MeOH solution to prepare the intermediate hemiketal, protection of the diol system that was formed during the key reaction, and finally oxidation of the hemiketal into the desired lactone **43** in 68% overall yield using *m*-chloroperbenzoic acid (*m*-CPBA) (1.1 equiv)/$BF_3{\cdot}OEt_2$ (0.1 equiv) conditions (scheme 16) [21].

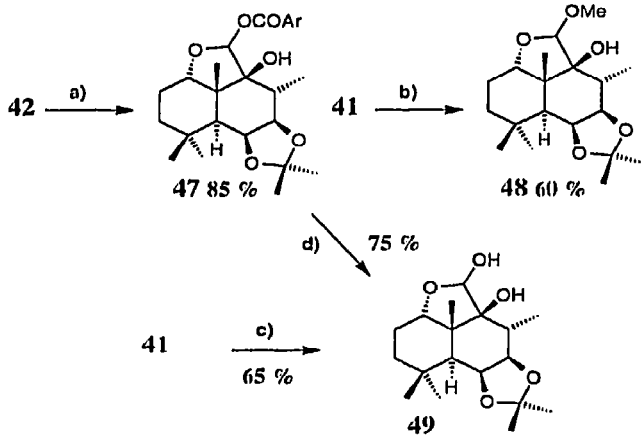


a) LDA, THF or KH, THF.

Scheme 16

Unfortunately starting from lactone **43** we were then unable to generate the α-selenide compound **45** or the corresponding lithio **46** derivative using lithium diisopropylamide (LDA) or KH base to introduce the double bond at C8-C9.

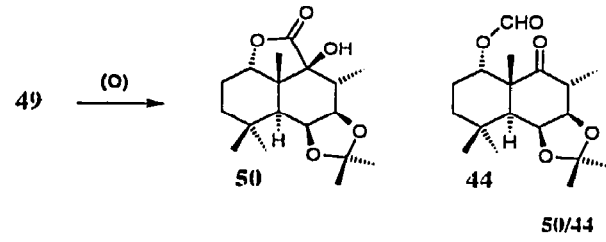
In order to introduce a hydroxyl function at the C9 position and prepare the α-hydroxylactone **50**, the dihydrofuran product **42** was oxidized with *m*-CPBA. In CH_2Cl_2 solution, the reaction led to ester **47**. Transformation of **41** into hemiketal **48** was also performed in 60% yield (scheme 17). Starting from the ester derivative **47**, a LAH reduction afforded the lactol **49** in 75% yield. Lactol **49** was not reduced even if an excess of LAH was used. Lactol **49** was also prepared in 65% yield directly from diol **41**.



a) *m*-CPBA, CH_2Cl_2, 20 °C, 12 h, 85%. b) (i) *m*-CPBA, CH_2Cl_2, 20 °C, 1 h, then HCl 1N/THF, 20 °C, 1 h, 68%. (ii) Amberlist $15H^+$, MeOH, 20 °C, 12 h, 95%. (iii) PPTS, 2-methoxypropene, 20 °C, 3 h 95%, 61% overall. c) (i) *m*-CPBA, CH_2Cl_2, 20 °C, 1 h, then HCl 1N/THF, 20 °C, 1 h, 68%. (ii) PPTS, 2-methoxypropene, 20 °C, 3 h, 95%, 65% overall. d) LAH, THF, 0 °C, 1 h, 75%.

Scheme 17

From lactol **49**, we again had to perform an oxidation reaction for the preparation of the hydroxylactone **50**. As observed previously, oxidation with PCC as well as the Dess–Martin reagent gave quantitatively the formylketone **44** (scheme 18). When Jones [22] and Fetizon [23] reagents were employed hydroxylactone **50** was obtained together with **44** in respectively 60:40 and 25:75 ratios. The best reagent we found in this case was



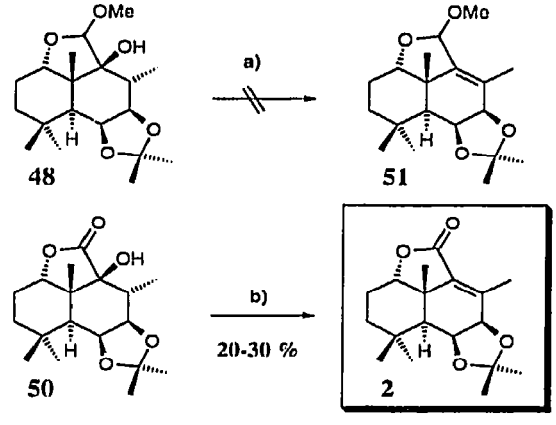
A) PCC (3 equiv), CH_2Cl_2, 20 °C, 3 h, >95% 0:100; B) Dess–Martin reagent (1.5 equiv), CH_2Cl_2, 20 °C, 1 h, >95% 0:100; C) Jone reagent (1.5 equiv), acetone, 0 °C, 90% 60:40; D) Ag_2CO_3 (10 equiv), toluene, Δ, 3 h, 85% 25:75; E) IBX (10 equiv), DMSO, 20 °C, 1 h, >95% 85:15.

Scheme 18

the IBX periodinane oxidant which gave lactone **50** and formylketone **44** in quantitative yield and in a 85:15 ratio.

^1H NMR studies with the aid of NOE experiments indicated that the 9-hydroxyl function of **50** had β-stereochemistry. Here again *m*-CPBA added on the β-side of the dihydrofuran function due to the concave structure of the molecule.

For the last step of the synthesis of lactone **2**, elimination of the 9β-hydroxyl, which has a *cis* relationship with the 8β-hydrogen, led us to perform appropriate *cis* elimination reactions. No elimination occurred and compound **51** was not obtained from hemiketal **48** using $MsCl/NEt_3/ClCH_2CH_2Cl/\Delta$ [24], or $SOCl_2$/pyridine/Δ [25], $POCl_3/\Delta$ [26], DMSO/Δ [27], or Burgess reagent/benzene/Δ [28] conditions (scheme 19).

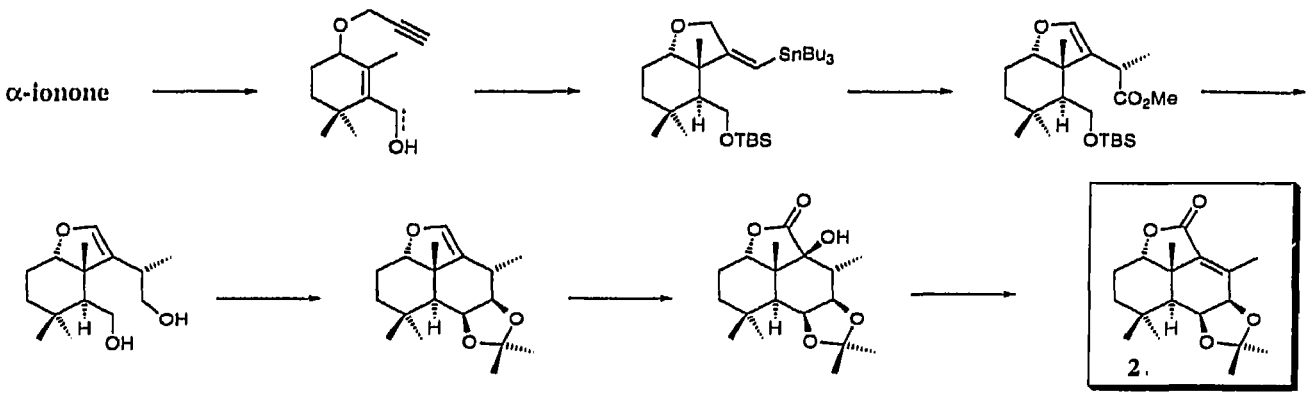


a) $POCl_3$, pyridine, Δ, or MsCl, NEt_3, Δ, or $SOCl_2$, pyridine, Δ. b) $SOCl_2$, pyridine, Δ, 0.5 h, 20–30%.

Scheme 19

Nevertheless after treatment of lactone **50** with $SOCl_2$/pyridine/Δ the expected conjugated lactone was produced in 20–30% yield. ^1H NMR data are identical to those reported by Ikegami, Corey [2a-c] and Ruveda [29]. The preparation of unsaturated lactone **2** gave us a formal synthesis of (±)-forskolin **1**.

During this work the total synthesis of **2** was realized from α-ionone in 17 steps (scheme 20) in a 1.3% overall yield.



17 steps 1.3 % overall yield

Scheme 20

Experimental section

Physical data and spectroscopic measurements

Melting points were determined with a Reichert apparatus and are uncorrected. Boiling points are uncorrected. Infrared spectra were obtained on a Perkin-Elmer FT 1600 instrument using either NaCl salt plates (film) or NaCl cell (in the specified solvent) and are reported in terms of frequency of absorption (ν, cm^{-1}).

^1H NMR spectra were recorded with a Bruker WP 200 (200 MHz) or a Bruker AM 400 (400 MHz) instrument. The solvent and the instrument are specified for each product. The chemical shifts are expressed in parts per million (ppm) referenced to residual chloroform at 7.28 ppm. Data are reported as follows: chemical shift, multiplicity (recorded as s (singlet), d (doublet), t (triplet), q (quartet) and m (multiplet)), integration, coupling constants (J) in hertz (Hz) and assignment. $^1H,^1H$-COSY and $^1H,^1H$-NOESY experiments were routinely carried out to ascertain ^1H-^1H connectivities and configuration assignments, respectively.

^{13}C NMR spectra were recorded with the same instruments 50.3 and 100.6 MHz respectively. The chemical shifts are given in parts per million (ppm), the central peak of deuterochloroform being referenced at 77.14 ppm. J-modulated spin-echo technique (J-mod) experiments were used for the determination of CH multiplicities. When necessary, ^{13}C NMR spectra were assigned with the aid of HETCOR experiments.

Mass spectra were obtained with a Hewlett Packard HP5989B spectrometer via either direct introduction or GC-MS, by chemical ionization (CI) with ammonia (NH_3) or methane (CH_4) or by electronic impact (EI). Microanalyses were performed by the analytical laboratory of the Institut de chimie des substances naturelles in Gif-sur-Yvette.

Usual procedures

All non-aqueous reactions were conducted under argon, in oven (120 °C) or flame-dried glassware.

Organolithium reagents were titrated using the procedure of Watson and Eastham [30]. The solution to be titrated was added dropwise via a syringe at 0 °C in a well-dried 25 mL round-bottomed flask containing a well-stirred solution of 1,2-phenanthroline or 2,2′-biquinoline (ca 5 mg), THF or diethyl ether (10 mL) and anhydrous benzyl alcohol (0.5 mL, 4.8 mmol). The addition was stopped after the colorless mixture turned dark red.

Bulb-to-bulb distillations were performed with a Büchi GKR 51 Kugelrohr apparatus.

Solvent distillation

Tetrahydrofuran, diethyl ether, benzene and toluene were distilled over sodium benzophenone. Dichloromethane and amines were distilled over calcium hydride. DMF was distilled from magnesium sulfate under reduced pressure. Ethanol and methanol were distilled over magnesium.

Chromatography

Thin layer chromatography (TLC) was performed on precoated plate of silica gel 60F 254 (Merck). Visualization was accomplished with UV light then 7–10% ethanolic phosphomolybdic acid solution followed by heating was used as developing agent.

Flash chromatography was performed on silica gel Merck SI 60 (0.040–0.063 mm). The solvents used were not distilled except petroleum ether.

^1H and ^{13}C NMR of organostannyl compounds

For large Sn-^1H or Sn-^{13}C coupling constants (250–450 Hz), the central signal was associated with two close pairs of satellites corresponding to both ^{117}Sn and ^{119}Sn isotopes; in this case two different coupling constants were reported. For small Sn-^1H and Sn-^{13}C (<100 Hz), the two pairs of satellites collapse and only one coupling constant was observed.

Nomenclature

IUPAC nomenclature was used for all compounds. Because racemic derivatives were described the relative stereochemistry was expressed using asterisks, and the first stereocenter assigned as R^*. In some cases and to be in agreement with the forskolin numbering 5α-H and 5β-H assignments were used.

(2aR,3S*,5R*,5aS*,8aS*,8bR*)-4-Methylidene-3,6,6,8b-tetramethyldecahydronaphtho[1,8-bc]furan-5-ol 11*

To a solution of alcohol 8 (87 mg, 0.37 mmol) in boiling toluene (38 mL) was added over 6 h, using a syringe pump,

a solution of Bu_3SnH (120 mL, 0.45 mmol, 1.2 equiv) and AIBN (6 mg, 0.04 mmol, 0.1 equiv) in toluene (90 mL). The reaction mixture was then concentrated in vacuo and purification by flash chromatography on basic silica gel gave compound **11** (40 mg, 46% yield) and starting material **8** (35 mg, 40% yield).

IR: (NaCl) ν cm^{-1} 3 410, 3 045, 2 990, 2 925, 1 655, 1 376, 1 265, 1 056, 855.

^1H NMR: ($CDCl_3$, 200 MHz, NOE experiments, forskolin numbering) δ 1.05 (d, J = 6.8 Hz, 3H, CH_3, CH_3-8), 1.12, 1.13 and 1.25 (3s, 9H, $3CH_3$, $2CH_3$-4, CH_3-10), 0.93–2.03 (m, 3H, Ha-2, H_2-3), 1.35 (d, J = 11.7 Hz, 1H, H-5), 1.64 (d, J = 6.5 Hz, 1H, OH), 2.0 (m, 2H, H-9, Hb-2), 2.56 (m, 1H, H-8), 3.55 (dd, J = 11.3, 8.1 Hz, 1H, Ha-11), 3.75 (dd, J = 8.1, 5.5 Hz, 1H, Hb-11), 3.75 (dd, J = 7.0, 5.5 Hz, 1H, H-1), 4.23 (dd, J = 11.7, 6.5 Hz, 1H, H-6), 4.76 (d, J = 1.6 Hz, 1H, Ha-1′), 5.16 (d, J = 1.6 Hz, 1H, Hb-1′).

^{13}C NMR: ($CDCl_3$, 50.3 MHz, forskolin numbering) δ 17.7 (CH_3-8), 21.8 (CH_3), 24.1 (CH_3), 25.7 (C-3), 32.9 (C-4), 32.9 (CH_3), 33.5 (C-9), 36.2 (C-2), 45.1 (C-10), 48.4 (C-8), 56.2 (C-5), 67.4 (C-11), 72.5 (C-6), 85.4 (C-1), 103.9 (C-1′), 155.0 (C-7).

MS: (CI, NH_3) m/z 268 ($MH^+ + NH_3$), 251 (MH^+), 250, 235, 217, 206, 189, 165.

Anal calc for $C_{16}H_{26}O_2$, 250.37: C, 76.75; H, 10.47. Found; C, 76.82; H, 10.38.

(3Z,2aR,4S*,4aR*,7aR*,7bR*)-5,5,7b-Trimethyl-3-[(trimethylsilyl)methylidene]-2a-vinyl-decahydro-indeno[7,1-bc]furan-4-ol* **12**

To a solution of alcohol **9** (74 mg, 0.25 mmol) in boiling toluene (25 mL) was added over 6 h, using a syringe pump, a solution of Bu_3SnH (250 mL, 0.91 mmol, 3.6 equiv) and AIBN (4 mg, 0.03 mmol, 0.1 equiv) in toluene (91 mL). The reaction mixture was concentrated in vacuo and purification by flash chromatography on basic silica gel gave **12** (7 mg, 10% yield) and recovered alcohol **9** (52 mg, 70%).

IR (CCl_4) ν 3 592, 3 412, 3 083, 2 957, 2 856, 1 618, 1 463, 1 381, 1 157, 1 086, 1 011, 854.

^1H NMR: ($CDCl_3$, 200 MHz, NOE experiments) δ 1.12 (s, 9H, $3CH_3$, $Si(CH_3)_3$], 1.07 (s, 3H, CH_3), 1.13 (2s, 6H, $2CH_3$), 0.80–2.01 (m, 6H, OH, H-4a, H_2-6, H_2-7), 1.50 (d, J = 12.2 Hz, 1H, OH), 3.29 (t, J = 3.1 Hz, 1H, H-7a), 3.70 (d, J = 8.5 Hz, 1H, Ha-2), 3.83 (d, J = 8.5 Hz, 1H, Hb-2), 4.54 (ddd, J = 12.2, 9.8, 2.7 Hz, 1H, H-4), 4.98 (dd, J = 17.7, 1.2 Hz, 1H, Ha-2″), 5.24 (dd, J = 11.2, 1.2 Hz, 1H, Hb-2″), 5.45 (d, J = 2.7 Hz, 1H, H-1′), 5.69 (dd, J = 17.7, 11.2 Hz, 1H, H-1″).

^{13}C NMR: ($CDCl_3$, 50.3 MHz) δ 0.8 ($3CH_3$, $Si(CH_3)_3$), 23.0 (C-6), 25.4 (CH_3), 25.9 (CH_3), 29.2 (C-7), 31.1 (CH_3), 33.0 (C-5), 50.4 (C-7b), 62.5 (C-4a), 65.5 (C-2a), 76.3 (C-4), 78.8 (C-2), 83.9 (C-7a), 114.8 (C-2″), 123.8 (C-1″), 139.8 (C-1′), 169.9 (C-3).

MS: (CI, NH_3) m/z 338 ($MH^+ + NH_3$), 321 (MH^+), 320, 303, 285, 267, 231, 213.

(4Z,2aR,3S*,5aS*,8aS*,8bR*)-3,6,6,8b-Tetramethyl-4-[(tributylstannyl)methylidene]decahydronaphtho-[1,8-bc]furan-5-one* **13**

To a solution of ketone **10** (60 mg, 0.3 mmol) in boiling toluene (40 mL) was added over 6 h, using a syringe pump, a solution of Bu_3SnH (125 μL, 0.47 mmol, 2 equiv) and AIBN (4 mg, 0.04 mmol, 0.1 equiv) in toluene (94 mL). The reaction mixture was concentred in vacuo and purification by flash chromatography on hydrogenated carbonated silica gel gave compound **13** (77 mg, 55% yield) and ketone **10** (21 mg, 35% yield).

IR: (NaCl) ν 3 410, 3 045, 2 990, 2 925, 1 705, 1 655, 1 620 1 376, 1 265, 1 056, 855.

^1H NMR: ($CDCl_3$, 200 MHz, NOE experiments, forskolin numbering) δ 0.90 {t, J = 6.0 Hz, 9H, $3CH_3$, $Sn((CH_2)_3CH_3)_3$}, 0.91 {t, J = 6.0 Hz, 6H, $3CH_2$, $Sn[CH_2(CH_2)_2CH_3]_3$}, 1.08, 1.11 and 1.18 (3s, 9H, $3CH_3$, $2CH_3$-4, CH_3-10), 1.18 (d, J = 7.0 Hz, 3H, CH_3, CH_3-8), 1.32–1.52 [m, 12H, $6CH_2$, $Sn(CH_2CH_2CH_2CH_3)_3$], 1.42–1.83 (m, 4H, H_2-2, H_2-3), 2.31 (q, J = 9.0 Hz, 1H, H-9), 2.36 (s, 1H, H-5), 3.01 (qdd, J = 7.0, 9.0, 1.9 Hz, 1H, H-8), 3.68 (t, J = 2.7 Hz, 1H, H-1), 3.97 (dd, J = 14.3, 9.0 Hz, 1H, Ha-11), 4.01 (dd, J = 14.3, 9.0 Hz, 1H, Hb-11), 6.31 (d, J = 1.9 Hz, 1H, H-1′, J H-^{117}Sn = J H-^{119}Sn = 61.0 Hz).

^{13}C NMR: ($CDCl_3$, 50.3 MHz, forskolin numbering) δ 11.4 ($3CH_2$, $Sn(CH_2CH_2CH_2CH_3)_3$, J ^{13}C-^{117}Sn = 342.0 Hz, J ^{13}C-^{119}Sn = 339.0 Hz), 13.9 ($3CH_3$, $Sn((CH_2)_3CH_3)_3$], 18.9, 20.1 and 21.0 ($3CH_3$), 22.4 (C-3), 27.5 ($3CH_2$, $Sn(CH_2CH_2CH_2CH_3)_3$, J ^{13}C-^{117}Sn = J ^{13}C-^{119}Sn = 58.0 Hz), 29.4 ($3CH_2$, $Sn(CH_2CH_2CH_2CH_3)_3$, J ^{13}C-^{117}Sn = J ^{13}C-^{119}Sn = 23.0 Hz), 31.8 (C-4), 32.2 (CH_3) 35.5 (C-9), 36.2 (C-2), 45.0 (C-10), 52.9 and 54.6 (C-5, C-8), 67.8 (C-11), 84.0 (C-1), 141.0 (C′-1, J ^{13}C-^{117}Sn = 363.0 Hz, J ^{13}C-^{119}Sn = 360.0 Hz), 156.0 (C-7), 202.4 (C-6).

MS: (CI, NH_3) m/z for major ^{120}Sn isotope 556 ($MH^+ + NH_3$), 538 (MH^+), 291.

(3aR,4R*S*,7aR*)-3a,5,5-Trimethyl-3-methylidene-octahydrobenzofuran-4-carbaldehyde* **15**

To a solution of PCC (2.3 g, 11 mmol, 1.5 equiv) and celite (2.3 g) in dichloromethane (20 mL) was added via cannula a solution of alcohol **14a** [3] (1:1 mixture of 5α-H and 5β-H isomers, 1.5 g, 7.1 mmol) in dichloromethane (15 mL). The resulting dark-brown solution was stirred at 20 °C for 1.5 h and filtered through a plug of celite and concentrated in vacuo. Purification by flash chromatography on silica gel gave a 1:1 mixture of 5α-H and 5β-H aldehyde **15** (1.4 g, 95% yield).

To a solution of the preceding 1:1 mixture of aldehyde **15** (500 mg, 2.4 mmol) in methanol (2 mL) was added K_2CO_3 (1.7 g, 12 mmol, 5 equiv) and the resulting suspension was stirred at reflux for 3 h and then cooled at 20 °C. The reaction mixture was partitioned between a 1 N aqueous HCl solution (20 mL) and diethyl ether (50 mL) and the phases were separated. The aqueous phase was extracted with diethyl ether (3 × 50 mL) and the combined organic phases were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. Purification by flash chromatography on silica gel gave the pure 5α-H aldehyde **15** (460 mg, 92% yield).

- *Compound* **15** *(5α-H)*

IR: ($CHCl_3$) ν 2 935, 2 852, 2 736, 1 715, 1 662, 1 461, 1 385, 1 367, 1 074, 1 051, 1 030, 891.

^1H NMR ($CDCl_3$, 400 MHz) δ 0.94, 1.17 and 1.27 (s, 9H, $2CH_3$-5, CH_3-3a), 1.12–1.90 (m, 4H, H_2-6, H_2-7), 2.01 (d, J = 3.8 Hz, 1H, H-4), 3.51 (t, J = 2.9 Hz, 1H, H-7a), 4.28 (td, J = 13.7, 2.4 Hz, 1H, Ha-2), 4.59 (td, J = 13.7, 2.4 Hz, 1H, Hb-2), 4.73 (t, J = 2.4 Hz, 1H, Ha-1′), 4.91 (t, J = 2.4 Hz, 1H, Hb-1′), 9.86 (d, J = 3.8 Hz, 1H, H-1″).

^{13}C NMR: ($CDCl_3$, 50.3 MHz) δ 17.9 (CH_3), 22.1 (CH_3), 22.2 (C-6), 32.2 (CH_3), 32.8 (C-5), 34.9 (C-7), 45.5 (C-3a), 58.5 (C-4), 69.8 (C-2), 84.2 (C-7a), 104.9 (C-1′), 156.6 (C-3), 204.9 (C-1″).

MS: (CI, NH_3) *m/z* 226 ($MH^+ + NH_3$), 209 (MH^+), 191, 179, 163, 153, 135, 123.

Anal calc for $C_{13}H_{20}O_2$, 208.29: C, 74.96; H, 9.68. Found; C, 74.59; H, 9.61.

• *Compound* **15** *(5β-H)*

IR ($CHCl_3$) ν 2 930, 2 850, 2 735, 1 715, 1 660, 1 460, 1 385, 1 370, 1 075, 1 060, 1 030, 890.

^1H NMR ($CDCl_3$, 200 MHz) δ 0.90, 1.09 and 1.33 (3s, 9H, $3CH_3$, CH_3-3a, 2 CH_3-5), 1.19–2.00 (m, 5H, H-4, H_2-6, H_2-7), 3.61 (t, J = 3.2 Hz, 1H, H-7a), 4.27 (dt, J = 14.1, 2.4 Hz, 1H, Ha-2), 4.33 (dt, J = 14.1, 2.4 Hz, 1H, Hb-2), 4.87 (t, J = 2.4 Hz, 1H, Ha-1′), 4.97 (t, J = 2.4 Hz, 1H, Hb-1′), 9.60 (d, J = 6.3 Hz, 1H, H-1″).

^{13}C NMR: ($CDCl_3$, 50.3 MHz) δ 22.9 (C-6), 26.3, 29.4 and 29.9 ($2CH_3$-5, CH_3-3a), 31.5 (C-7), 32.1 (C-5), 46.1 (C-3a), 66.8 (C-4), 70.5 (C-2), 83.2 (C-7a), 106.4 (C-1″), 156.2 (C-3), 204.8 (C-1′).

MS (CI, NH_3) *m/z* 226 ($MH^+ + NH_3$), 209 (MH^+), 191, 179, 163, 153, 135, 123.

(3aR,4R*,7aR*)-1-(3a,5,5-Trimethyl-3-methylidene-octahydrobenzofuran-4-yl)prop-2-yn-1-one* **16**

To a cooled solution (0 °C) of lithium acetylide–ethylenediamine complex (1.7 g, 19 mmol, 2.5 equiv) in 15 mL of THF was added aldehyde **15** (5α-H) (1.5 g, 7.2 mmol) in THF (5 mL). The reaction mixture was stirred at this temperature for 3 h and then at 20 °C for 12 h. The reaction was quenched with an saturated aqueous NH_4Cl solution (10 mL) and diluted with diethyl ether (50 mL). The phases were separated and the aqueous phase was extracted with diethyl ether (3 × 50 mL). The combined organic phases were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. Purification by flash chromatography on silica gel gave [1*R**(3a*S**,4*S**,7a*S**)]-1-(3-methylidene-3a,5,5-trimethyloctahydrobenzofuran-4-yl)prop-2-yn-1-ol (1.27 g, 75% yield).

IR: (NaCl) ν 3 607, 3 417, 3 304, 2 937, 2 859, 1 419, 2 340, 2 156, 1 659, 1 461, 1 370, 1 075, 1 048, 1 029, 908, 737.

^1H NMR ($CDCl_3$, 200 MHz) δ 1.24 and 1.36 (3s, 9H, $3CH_3$, $2CH_3$-5′, CH_3-3′a), 1.06–1.87 (m, 4H, H_2-6′, H_2-7′), 1.66 (d, J = 1.2 Hz, 1H, H-4′), 2.27 (d, J = 6.6 Hz, 1H, OH), 2.55 (d, J = 2.5 Hz, 1H, H-3), 3.52 (t, J = 2.8 Hz, 1H, H-7′a), 4.28 (dd, J = 13.3, 2.0 Hz, 1H, Ha-2′), 4.58 (dd, J = 13.3, 2.0 Hz, 1H, Hb-2′), 4.91 (ddd, J = 6.6, 2.5, 1.2 Hz, 1H, H-1), 5.02 (d, J = 2.0 Hz, 1H, Ha-1″), 5.03 (d, J = 2.0 Hz, 1H, Hb-1″).

^{13}C NMR: ($CDCl_3$, 50.3 MHz) δ 17.8, 23.8 and 33.6 ($3CH_3$, $2CH_3$-5′, CH_3-3′a), 22.6 (C-6′), 34.9 (C-5′), 37.9 (C-7′), 48.2 (C-3′a), 50.6 (C-4′), 61.9 (C-1), 69.8 (C-2′), 74.2 (C-3), 85.3 (C-7′a), 87.7 (C-2), 105.6 (C-1″), 159.2 (C-3′).

MS: (CI, NH_3) *m/z* 252 ($MH^+ + NH_3$), 235 (MH^+), 217, 199, 189, 175, 161, 147, 123, 109.

Anal calc for $C_{15}H_{22}O_2$, 234.33: C, 76.88; H, 9.46. Found; C, 76.95; H, 9.38.

A solution of the above alcohol (300 mg, 1.3 mmol) in 3 mL of dichoromethane was added at 20 °C to a solution of the Dess–Martin reagent (100 mg, 2 mmol, 1.5 equiv) in 2 mL of dichloromethane. The reaction was stirred at 20 °C for 1 h and quenched with 5 mL of a saturated aqueous Na_2SO_3 solution. The mixture was diluted with 25 mL of diethyl ether and the phases were separated. The aqueous phase was extracted with 3 × 25 mL of diethyl ether and the combined organic phases were washed with saturated aqueous $NaHCO_3$, then with brine, dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. Purification by flash chromatography on silica gel gave ketone **16** (110 mg, 86% yield).

IR ($CHCl_3$) ν 3 298, 2 938, 2 857, 2 158, 1 182, 1 674, 1 462, 1 391, 1 370, 1 336, 1 140, 1 159, 1 103, 1 087, 1 048, 1 030, 908, 754, 649.

^1H NMR: ($CDCl_3$, 200 MHz) δ 1.03, 1.13 and 1.25 (3s, 9H, $3CH_3$, $2CH_3$-5′, CH_3-3′a), 1.23 (m, 1H), 1.65 (m, 1H), 1.85 (m, 2H), 2.89 (s, 1H, H-3), 3.21 (s, 1H, H-4′), 3.53 (t, J = 2.5 Hz, 1H, H-7′a), 4.32 (dt, J = 13.7, 2.1 Hz, 1H, Ha-2′), 4.61 (dt, J = 13.7, 2.1 Hz, 1H, Hb-2′), 4.77 (t, J = 2.1 Hz, 1H, Ha-1″), 4.89 (t, J = 2.1 Hz, 1H, Hb-1″).

^{13}C NMR: ($CDCl_3$, 50.3 MHz) δ 18.1 (CH_3), 22.0 (C-6′), 22.2 (CH_3), 32.4 (CH_3), 34.8 (C-5′), 35.3 (C-7′), 46.5 (C-3a′), 61.4 (C-4′), 69.6 (C-2′), 77.4 (C-3), 84.1 (C-7′a), 85.5 (C-2), 104.5 (C-1″), 156.3 (C-3′), 190.1 (C-1).

MS: (CI, NH_3) *m/z* 250 ($MH^+ + NH_3$), 233 (MH^+), 215, 213, 187, 175, 159, 147, 133, 123, 109.

Anal calc for $C_{15}H_{20}O_2$, 232.31: C, 77.55; H, 8.68. Found; C, 77.75; H, 8.61.

(2R/S*,3aS*,4S*,7aS*)-1-(2-Ethoxy-3a,5,5-trimethyl-3-methylidene-octahydrobenzofuran-4-yl)prop-2-yn-1-one* **17**

To a solution of selenium dioxide (60 mg, 0.5 mmol, 2.5 equiv) in dioxane (5 mL) was added distilled water (28 μL) and the resulting mixture was stirred at 20 °C for 15 min. A solution of compound **16** (50 mg, 0.2 mmol) in dioxane (1 mL) was transferred to the above solution and the reaction mixture was stirred at reflux for 5 h. After cooling to 20 °C, the heterogeneous solution was filtered over a plug of celite and the solid rinsed with diethyl ether (50 mL).

To a solution of the above crude residue (7 mg, 0.03 mmol) in ethanol (1 mL) was added Amberlist resin (20 mg). The resulting suspension was stirred at 20 °C for 2 h, filtered over celite and the filtrate rinsed with 50 mL of diethyl ether. The organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The resulting oil was purified by flash chromatography (elution petroleum ether/ethyl acetate) to afford 7 mg (13% yield) of the title compound **17**.

IR: ($CHCl_3$) ν 2 943, 2 875, 2 154, 1 181, 1 673, 1 468, 1 391, 1 370, 1 336, 1 140, 1 121, 1 031, 754.

^1H NMR ($CDCl_3$, 200 MHz) δ 1.00, 1.10, (2s, 6H, $2CH_3$), 1.25 (t, J = 6.5 Hz, 3H, CH_3, OCH_2CH_3), 1.27 (s, 3H, CH_3), 1.61–1.93 (m, 4H, H_2-6′, H_2-7′), 2.80 (s, 1H, H-3) 3.20 (s, 1H, H-4′), 3.45 (m, 2H, OCH_2CH_3), 3.82 (broad s, 1H, H-7′a), 4.97 (d, J = 1.8 Hz, 1H, H-1″a), 5.24 (d, J = 1.8 Hz, 1H, H-1″b), 5.53 (t, J = 1.8 Hz, 1H, H-2′).

^{13}C NMR: ($CDCl_3$, 50.3 MHz) δ 15.5 (CH_3, OCH_2CH_3), 17.9 (CH_3), 21.7 (C-6′), 29.8 (CH_3), 32.4 (CH_3), 34.8 (C-5′), 35.3 (C-7′), 46.6 (C-3′a), 62.7 (C-4′), 64.2 (CH_2, OCH_2CH_3), 77.8 (C-3), 82.0 (C-7a′), 86.0 (C-2), 103.0 (C-1″), 110.8 (C-2′), 157.5 (C-3′), 190.50 (C-1).

MS: (CI, NH_3) *m/z* 294 ($MH^+ + NH_3$), 277 (MH^+).

(3aR,4R*,7aR*)-3a,5,5-Trimethyl-3-methylidene-4-{[(triphenylmethyl)oxy]methyl} hexahydrobenzofuran-2-one* **19**

To a solution of selenium dioxide (60 mg, 0.5 mmol, 2.5 equiv) in dioxane (5 mL) was added distilled water (28 μL) and the resulting mixture was stirred at 20 °C for 15 min. A solution of compound **14b** [3] (91 mg, 0.2 mmol) in dioxane (1 mL) was transferred to the above solution and the reaction mixture was stirred at reflux for 5 h. After cooling to 20 °C, the heterogeneous solution was filtered over celite and the solid was rinsed with diethyl ether (50 mL)

and concentrated in vacuo to give compound **19** (63 mg, 67% yield).

IR ($CHCl_3$) ν 2 948, 1 663, 1 550, 1 448, 1 054, 909, 733, 649.

^1H NMR ($CDCl_3$, 200 MHz) δ 0.75–1.85 (m, 5H, H-4, H_2-6, H_2-7), 0.48 (s, 3H, CH_3), 0.96 (s, 3H, CH_3), 1.22 (s, 3H, CH_3), 3.27 (dd, J = 10.5, 7.0 Hz, 1H, Ha-1″), 3.35 (dd, J = 10.5, 2.0 Hz, 1H, Hb-1″), 4.20 (t, J = 6.5 Hz, 1H, H-7a), 4.80 (s, 1H, Ha-1′), 5.89 (s, 1H, Hb-1′), 7.32 (m, 9H, Ar-H), 7.51 (m, 6H, Ar-H).

^{13}C NMR: ($CDCl_3$, 50.3 MHz) δ 17.1 (CH_3-2a), 23.3 (C-6), 31.3 and 32.1 (2CH_3-5), 34.2 (C-5), 35.0 (C-7), 44.7 (C-3a), 51.6 (C-4), 61.6 (C-1″), 85.4 (C-7a), 87.5 [*C*(Ph)$_3$], 122.5 (C-1′), 127.2 (3CH, Ar), 127.9 (6CH, Ar), 128.8 (6CH, Ar), 144.0 (3C, Ar), 144.3 (C-3), 165.2 (C-2).

MS: (CI, NH_3) m/z 484 ($MH^+ + NH_3$), 467 (MH^+).

(2R/S*,3aS*,4S*,7aS*)-2-Methoxy-3a,5,5-trimethyl-3-methylidene-4-{[(triphenylmethyl)oxy]methyl}-octahydrobenzofuran* **20**

To a solution of **19** (50 mg, 0.1 mmol) in toluene (3 mL) cooled to −20 °C was added a 1.5 M DIBALH solution in toluene (360 µL, 0.54 mmol, 5 equiv). The reaction was stirred at this temperature for 1 h and quenched with methanol (0.5 mL). The reaction mixture was partitioned between water (10 mL) and diethyl ether (30 mL). The phases were separated and the aqueous layer was extracted with diethyl ether (3 × 25 mL). The combined organic phases were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo to give the corresponding lactol which was carried on to the next step without further purification.

To a solution of the above lactol in methanol (2 mL) was added 15H$^+$ Amberlist resin (80 mg). The resulting suspension was stirred at 20 °C for 2 h, filtered over celite and the filtrate was rinsed with 50 mL of diethyl ether. The organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The resulting oil was purified by flash chromatography (elution petroleum ether/ethyl acetate) to afford 7 mg (75% yield) of compound **20**.

IR: ($CHCl_3$) ν 2 948, 1 550, 1 448, 1 054, 909, 733, 649.

^1H NMR: ($CDCl_3$, 200 MHz) δ 0.75–1.85 (m, 5H, H-4, H_2-6, H_2-7), 0.71 (s, 3H, CH_3), 0.63 (s, 3H, CH_3), 0.96 (s, 3H, CH_3), 2.95 (dd, J = 10.5, 7.0 Hz, 1H, Ha-1″), 3.28 (dd, J = 10.5, 2.0 Hz, 1H, Hb-1″), 3.39 (s, 3H, OCH_3), 3.63 (t, J = 6.5 Hz, 1H, H-7a), 4.48 (s, 1H, Ha-1′), 5.0 (s, 1H, Hb-1′), 5.35 (s, 1H, H-2), 7.31 (m, 9H, ArH), 7.52 (m, 6H, ArH).

^{13}C NMR: ($CDCl_3$, 50.3 MHz) δ 17.7 (CH_3-2a), 22.8 (C-6), 22.5 and 34.2 (2CH_3-5), 33.4 (C-5), 35.0 (C-7), 47.6 (C-3a), 55.1 (C-4), 61.6 (C-1″), 62.5 (O-CH_3), 82.6 (C-7a), 87.7 [*C*(Ph)$_3$], 104.0 (C-2), 110.3 (C-1′), 127.7 (3CH, Ar), 129.1 (6CH, Ar), 129.3 (6CH, Ar), 144.6 (3C, Ar), 157.4 (C-3).

MS: (CI, NH_3) m/z 483 (MH^+), 244.

Anal calc for $C_{33}H_{38}O_3$, 482.63: C, 82.12; H, 7.94. Found: C, 82.28; H, 7.76.

(3aR,4R*,7aR*)-2-(4-Hydroxymethyl-3a,5,5-trimethyl-3a,4,5,6,7,7a-hexahydrobenzofuran-3-yl)propanenitrile* **22b**

To a solution of **22a** [3] (105 mg, 0.3 mmol) in acetonitrile (950 µL) at 20 °C was added a 48% aqueous HF solution (50 mL). The resulting cloudy mixture was stirred at 20 °C for 1 h, and the reaction quenched with a saturated aqueous $NaHCO_3$ solution (5 mL) and diluted with diethyl ether (30 mL). The phases were separated and the aqueous phase was extracted with diethyl ether (3 × 25 mL). The combined organic phases were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. Flash chromatography on silica gel gave alcohol **22b** (67 mg, 90% yield).

To a solution of **23** (50 mg, 0.2 mmol) in toluene (3 mL) cooled at −20 °C was added a 1.5 M DIBALH solution in toluene (0.7 mL, 1.0 mmol, 5 equiv). The reaction was stirred at this temperature for 1 h and quenched with methanol (0.5 mL). The reaction mixture was partitioned between water (10 mL) and diethyl ether (30 mL). The phases were separated and the aqueous layer was extracted with diethyl ether (3 × 25 mL). The combined organic phases were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo to give **22a** (38 mg, 75% yield).

IR: ($CHCl_3$) 3 300, 3 200, 2 934, 2 895, 2 220, 1 665, 1 621, 1 385, 1 090, 1 064, 864.

^1H NMR: ($CDCl_3$, 200 MHz) δ 0.77–1.85 (m, 5H, H_2-6′, H_2-7′, H-4′), 0.89 (s, 3H, CH_3), 1.03 (s, 3H, CH_3), 1.15 (s, 3H, CH_3), 1.35 (d, J = 7.8 Hz, 3H, CH_3-1′), 3.70 (dd, J = 11.1, 7.3 Hz, 1H, Ha-1″), 3.82 (dd, J = 11.1, 3.4 Hz, 1H, Hb-1″), 4.0 (q, J = 7.8 Hz, 1H, H-1), 4.25 (t, J = 3.6 Hz, 1H, H-7a′), 6.65 (s, 1H, H-2′).

MS (CI, NH_3): m/z 266 ($MH^+ + NH_3$), 250 (MH^+).

(3aR,4R*,7aR*)-2-(4-Formyl-3a,5,5-trimethyl-3a,4,5,6,7,7a-hexahydrobenzofuran-3-yl)propanenitrile* **23**

To a solution of **22b** in dichloromethane (1 mL) was added Dess-Martin reagent (170 mg, 0.6 mmol, 2 equiv) and the reaction mixture was stirred at 20 °C for 1.5 h, then partitioned between a saturated aqueous Na_2SO_3 solution (5 mL) and diethyl ether (30 mL) and the phases were separated. The aqueous phase was extracted with diethyl ether (3 × 25 mL) and the combined organic phases were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. Purification by flash chromatography on silica gel gave aldehyde **23** (55 mg, 79% yield).

IR: ($CHCl_3$) ν 3 014, 2 934, 2 219, 1 712, 1 638, 1 278, 1 143, 1 034.

^1H NMR ($CDCl_3$, 400 MHz) δ 0.84–2.05 (m, 4H, H_2-6′, H_2-7′), 1.02 (s, 3H, CH_3), 1.26 (s, 3H, CH_3), 1.33 (s, 3H, CH_3), 1.41 (d, J = 7.8 Hz, 3H, CH_3), 2.08 (d, J = 3.8 Hz, 1H, H-4′), 3.01 (dd, J = 19.2, 1.6 Hz, 1H, Ha-1), 3.47 (dd, J = 19.2, 1.6 Hz, 1H, Hb-1), 4.07 (t, J = 3.5 Hz, 1H, H-7′a), 6.44 (s, 1H, H-2′), 9.7 (d, J = 3.8 Hz, 1H, H-1″).

MS (CI, NH_3) m/z 248 (MH^+).

[2Z(3Z,3aR,4R*,7aR*)]-(4-Hydroxymethyl-3a,5,5-trimethyloctahydrobenzofuran-3-ylidene)-acetic acid methyl ester* **25**

To a solution of **24** [3] (590 mg, 1.5 mmol) in THF (5 mL) at 20 °C was added a 1 M TBAF solution in THF and the mixture was stirred at this temperature for 12 h. The reaction was quenched with water (10 mL), diluted with diethyl ether (50 mL) and the phases were separated. The aqueous phase was extracted with diethyl ether (3 × 25 mL) and the combined organic phases washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. Purification of the residue by flash chromatography on silica gel gave alcohol **25** (150 mg, 58% yield) as a yellow oil.

IR ($CHCl_3$) ν 3 464, 2 949, 2 856, 1 708, 1 658, 1 436, 1 350, 1 224, 1 177, 1 047, 1 019, 909, 733, 684.

^{1}H NMR: ($CDCl_3$, 200 MHz) δ 0.7–1.8 (m, 6H, H-4′, H_2-6′, H_2-4′, OH), 0.90, 1.0 and 1.03 (3s, 9H, $3CH_3$, CH_3-3′a, $2CH_3$-5′), 3.42 (t, J = 2.5 Hz, 1H, H-7′a), 3.62 (s, 3H, CH_3, CO_2CH_3), 3.70 (m, 2H, H_2-1″), 4.68 (dd, J = 17.5, 2.5 Hz, 1H, Ha-2′), 4.88 (dd, J = 17.5, 2.5 Hz, 1H, Hb-2′), 5.60 (t, J = 2.5, 1H, H-2).

^{13}C NMR: ($CDCl_3$, 50.3 MHz) δ: 16.3 (CH_3-3′a), 20.7 (C-6′), 21.1 (CH_3-5′), 32.2 (C-5′), 32.5 (CH_3-5′), 34.2 (C-7′), 47.2 (C-3′a), 48.0 (C-4′), 50.5 (CH_3, CO_2CH_3), 59.4 (C-1″), 69.4 (C-2′), 82.3 (C-7′a), 110.2 (C-2), 165.8 (C-3′), 171.5 (C-1, CO_2CH_3).

MS: (CI, NH_3): m/z 286 ($MH^+ + NH_3$), 269 (MH^+), 254, 181, 167, 153, 137, 123, 52.

[2Z(3Z,3aR,4R*,7aR*)]-(4-Formyl-3a,5,5-trimethylhexahydrobenzofuran-3-ylidene) acetic acid methyl ester* **26**

To a solution of oxalyl chloride (30 μL, 0.3 mmol, 1.5 equiv) in dichloromethane (200 μL) cooled at −60 °C was added DMSO (50 μL, 0.6 mmol, 3 equiv) in dichloromethane (200 μL). The reaction mixture was stirred at this temperature for 5 min and the alcohol **25** (60 mg, 0.2 mmol) added. Stirring was continued for 30 min and triethylamine (140 μL, 1.0 mmol, 5 equiv) added. The reaction was stirred for 5 min and allowed to warm to 20 °C over 2 h and quenched with water (10 mL), diluted with diethyl ether (50 mL) and the phases were separated. The aqueous phase was extracted with diethyl ether (3 × 25 mL) and the combined organic phases were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. Purification by flash chromatography on silica gel gave aldehyde ester **26** (44 mg, 83% yield) as a yellow oil.

IR: ($CHCl_3$) ν 2 960, 2 856, 1 735, 1 648, 1 438, 1 379, 1 261, 1 088, 910, 734.

^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.78–2.01 (m, 5H, H-4′, H_2-6′, H_2-4′), 0.90, 1.00 and 1.03 (3s, 9H, $3CH_3$, CH_3-3′a, 2 CH_3-5′), 3.44 (t, J = 2.5 Hz, 1H, H-7′a), 3.65 (s, 3H, CH_3, CO_2CH_3), 4.71 (dd, J = 17.5, 2.5 Hz, 1H, Ha-2′), 4.89 (dd, J = 17.5, 2.5 Hz, 1H, Hb-2′), 5.60 (t, J = 2.5, 1H, H-2), 9.82 (s broad, 1H, CHO).

^{13}C NMR: ($CDCl_3$, 50.3 MHz) δ 16.3 (CH_3-3′a), 20.7 (C-6′), 21.1 (CH_3-5′), 32.2 (C-5′), 32.5 (CH_3-5′), 34.2 (C-7′), 47.2 (C-3′a), 49.2 (C-4′), 50.5 (CH_3, CO_2CH_3), 69.6 (C-2′), 82.4 (C-7′a), 110.2 (C-2), 164.7 (C-3′), 171.5 (C-1, CO_2CH_3), 203.4 (CHO).

MS (CI, NH_3) m/z 284 ($MH^+ + NH_3$), 267 (MH^+), 181, 167, 153, 137, 127, 123.

(2aR,7aS*,7bR*)-(5,5,7b-Trimethyl-2a,5,6,7,7a,7b-hexahydro-2H-furo[2,3,4-cd]benzofuran-2a-yl) acetic acid methyl ester* **27**

To a solution of aldehyde **26** (230 mg, 0.91 mmol) in toluene (5 mL) was added DBU (1.34 mL, 9.0 mmol, 10 equiv) and the resulting mixture stirred at 65 °C for 4 h, cooled at 20 °C and partitioned between a 1 N aqueous HCl solution (10 mL) and diethyl ether (50 mL) and the phases were separated. The aqueous phase was extracted with diethyl ether (3 × 25 mL) and the combined organic phases were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. Purification by flash chromatography on silica gel gave compound **27** (156 mg, 65% yield) as a yellow oil.

IR ($CHCl_3$) ν 3 012, 2 953, 1 751, 1 466, 1 341, 1 189, 1 134, 1 021, 837.

^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.75–2.10 (m, 4H, H_2-6′, H_2-7′), 1.10 (s, 3H, CH_3), 1.11 (s, 3H, CH_3), 1.18 (s, 3H, CH_3), 2.55 (d, J = 15.6 Hz, 1H, Ha-2), 2.80 (d, J = 15.6 Hz, 1H, Hb-2), 3.67 (dd, J = 6.0, 3.0 Hz, 1H, H-7′a), 3.72 (s, 3H, CH_3, CO_2CH_3), 3.90 (d, J = 11.0 Hz, 1H, Ha-2′), 4.32 (d, J = 11.0 Hz, 1H, Hb-2′), 5.99 (s, 1H, H-4′).

^{13}C NMR: ($CDCl_3$, 50.3 MHz) δ 18.0 (CH_3), 24.1 (C-6′), 26.3 (CH_3), 30.3 (CH_3), 32.0 (C-5′), 36.0 (C-7′), 39.4 (C-2), 51.8 (CH_3, CO_2CH_3), 55.3 (C-7′b), 80.2 (C-2′), 83.5 (C-7′a), 94.7 (C-2′a), 124.8 (C-4′a), 137.6 (C-4′), 170.8 (C-1, CO_2CH_3).

MS: (CI, NH_3) m/z 284 ($MH^+ + NH_3$), 267 (MH^+).

Anal calc for $C_{15}H_{22}O_4$, 266.33: C, 67.64; H, 8.33. Found; C, 67.78; H, 8.29.

[2R(3aR*,4R*,7aR*]-2-(4-{[(tert-Butyldimethylsilyl)-oxy]methyl}-3a,5,5-trimethyl-3a,4,5,6,7,7a-hexahydrobenzofuran-3-yl)propanal* **32**

To a solution of alcohol **30** [3] (50 mg, 0.14 mmol) and pyridine (50 μL, 0.6 mmol, 4 equiv) in 1 mL of dichloromethane was added the Dess–Martin reagent (90 mg, 0.2 mmol, 1.5 equiv) and the reaction mixture was stirred at 20 °C for 1.5 h, then partitioned between a saturated Na_2SO_3 aqueous solution (5 mL) and diethyl ether (30 mL) and the phases were separated. The aqueous phase was extracted with diethyl ether (3 × 25 mL) and the combined organic phases were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. Purification by flash chromatography on silica gel gave aldehyde **32** (45 mg, 88% yield).

IR ($CHCl_3$) ν 3 021, 2 985, 1 721, 1 632, 1 381, 1 358, 1 123, 1 057, 936.

^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.02 (s, 6H, $2CH_3$, $Si(CH_3)_2$), 0.85–2.2 (m, 5H, H-4′, H_2-6′, H_2-7′), 0.95 (s, 9H, $3CH_3$, $SiC(CH_3)_3$), 1.02 (s, 3H, CH_3), 1.22 (s, 3H, CH_3), 1.40 (d, J = 6.5 Hz, 3H, CH_3-2), 1.45 (s, 3H, CH_3), 3.60 (q, J = 6.5 Hz, 1H, H-2), 3.91 (dd, J = 10.6, 2.5 Hz, 1H, Ha-1″), 4.05 (dd, J = 10.6, 7.3 Hz, 1H, Hb-1″), 4.18 (t, J = 3.6 Hz, 1H, H-7′a), 6.29 (s, 1H, H-2′), 9.78 (s broad, 1H, CHO).

^{13}C NMR: ($CDCl_3$, 50.3 MHz) δ −5.4 ($2CH_3$, $Si(CH_3)_2$), 17.6 (CH_3), 18.4 (C, $SiC(CH_3)_3$), 21.3 (CH_3), 22.7 (C-6′), 22.7 (CH_3), 26.1 ($3CH_3$, $SiC(CH_3)_3$), 32.3 (CH_3), 35.8 (C-5′), 36.3 (C-7′), 44.1 (C-2), 47.3 (C-3a′), 54.2 (C-4′), 61.7 (C-1″), 90.2 (C-7a), 126.7 (C-3′), 143.4 (C-2′), 200.4 (CHO).

MS: (CI, NH_3) m/z 384 ($MH^+ + NH_3$), 367 (MH^+).

(3R,3aR*,3bR*,4R*,7aR*,8aS*)-4-{[(tert-Butyldimethylsilyl)oxy]methyl}-3,3b,5,5-tetramethyldecahydrofuro[2,3-b]benzofuran* **33b**

A mixture of **30** (250 mg, 0.7 mmol), dimethyl sulfoxide (4 mL) and triethylamine (0.7 mL, 5 mmol) was stirred and treated with pyridine/sulfur trioxide complex SO_3-pyridine (540 mg, 3.4 mmol, 5 equiv) in dimethyl sulfoxide (3 mL) for 3 h at 20 °C. The reaction mixture was cooled to 0 °C and a 20% aqueous HCl solution was added before extraction with diethyl ether. Purification by flash chromatography on silica gel led to compound **33b** (183 mg, 72%).

IR ($CHCl_3$) ν 3 015, 2 960, 1 460, 1 345, 1 185, 1 155, 1 030, 850.

^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.05 (s, 6H, $2CH_3$, $Si(CH_3)_2$), 1.0–1.9 (m, 6H, H_2-6, H_2-7, H-4, H-3a), 0.90 (s, 9H, $2CH_3$, $SiC(CH_3)_3$), 0.94 (s, 3H, CH_3), 1.08 (s, 3H, CH_3), 1.10 (s, 3H, CH_3), 1.18 (d, J = 6.5 Hz, 3H, CH_3-3), 2.18 (m, 1H, H-3), 3.60 (dd, J = 9.0, 5.0 Hz, 1H, H-7a), 3.65 (dd, J = 10.5, 6.5 Hz, 1H, Ha-1′), 3.72 (dd, J = 10.5, 6.5 Hz, 1H, Hb-1′), 3.96 (ddd, J = 8.0, 7.0, 6.0 Hz, 1H,

Ha-2), 4.15 (ddd, J = 8.0, 7.0, 6.0 Hz, 1H, Hb-2), 5.62 (d, J = 4.5 Hz, 1H, H-8a).

MS: (CI, NH_3) m/z 386 ($MH^+ + NH_3$), 369 (MH^+).

(3R,3aR*,3bR*,4R*,7aR*,8aS*)-3,3b,5,5-Tetramethyl-4-{[(trimethylsilyl)oxy]methyl}-decahydrofuro[2,3-b]benzofuran* **33a** *and (3aR*,4R*,7aR*)-4-{[(trimethylsilyl)oxy]methyl}-3-((1R*)-1-{[(trimethylsilyl)oxy]methyl}ethyl)-3a,5,5-trimethyl-3a,4,5,6,7,7a-hexahydrobenzofuran* **34**

To a solution of diol **31** [3] (240 mg, 1.0 mmol) in CH_2Cl_2 (2 mL) and triethylamine (700 µL, 5 mmol, 5 equiv) cooled at 0 °C was added dropwise chlorotrimethylsilane (510 µL, 4.0 mmol, 4 equiv). After stirring at 0 °C for 1 h, the reaction mixture was allowed to warm to 20 °C and then stirred for 12 h at 20 °C. The reaction mixture was then partitioned between water (10 mL) and diethyl ether (50 mL) and the phases were separated. The aqueous phase was extracted with diethyl ether (3 × 25 mL) and the combined organic phases were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. Purification by flash chromatography on silica gel gave silylated alcohol **34** (194 mg, 50% yield) and the furofuran derivative **33a** (98 mg, 30% yield).

To a solution of oxalyl chloride (30 µL, 0.3 mmol, 1.5 equiv) in dichloromethane (200 µL) cooled at −60 °C was added DMSO (50 µL, 0.6 mmol, 3 equiv) in dichloromethane (200 µL). The reaction mixture was stirred at this temperature for 5 min and the bis-silylether **34** (80 mg, 0.2 mmol) added. Stirring was continued for 30 min and triethylamine (140 µL, 1.0 mmol, 5 equiv) was added. The reaction was stirred for 5 min and allowed to warm to 20 °C over 2 h and quenched with water (10 mL), diluted with diethyl ether (50 mL) and the phases were separated. The aqueous phase was extracted with diethyl ether (3 × 25 mL) and the combined organic phases were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. Purification by flash chromatography on silica gel gave **33a** (20 mg, 30% yield) as a yellow oil.

• *Compound* **33a**

IR: ($CHCl_3$) ν 3 026, 2 953, 1 466, 1 343, 1 178, 1 154, 1 021, 843.

^1H NMR ($CDCl_3$, 200 MHz) δ 0.12 (s, 9H, $3CH_3$, $Si(CH_3)_3$), 1.0–1.9 (m, 6H, H_2-6, H_2-7, H-4, H-3a), 0.93 (s, 3H, CH_3), 1.06 (s, 3H, CH_3), 1.09 (s, 3H, CH_3), 1.14 (d, J = 6.2 Hz, 3H, CH_3-3), 2.15 (m, 1H, H-3), 3.55 (dd, J = 9.0, 5.0 Hz, 1H, H-7a), 3.62 (dd, J = 10.2, 6.7 Hz, 1H, Ha-1′), 3.72 (dd, J = 10.2, 6.7 Hz, 1H, Hb-1′), 3.92 (ddd, J = 8.0, 7.0, 6.0 Hz, 1H, Ha-2), 4.11 (ddd, J = 8.0, 7.0, 6.0 Hz, 1H, Hb-2), 5.59 (d, J = 4.5 Hz, 1H, H-8a).

^{13}C NMR: ($CDCl_3$, 50.3 MHz) δ −0.1 ($3CH_3$, $Si(CH_3)_3$), 25.4 (C-6), 25.5 (CH_3), 25.7 (CH_3), 29.8 (C-3), 32.4 (C-5), 30.7 (CH_3), 33.1 (CH_3), 36.9 (C-7), 44.3 (C-3a), 47.1 (C-3b), 58.2 (C-4), 61.4 (C-1′), 69.6 (C-2), 85.6 (C-7a), 107.3 (C-8a).

MS: (CI, NH_3) m/z 344 ($MH^+ + NH_3$), 327 (MH^+).

• *Compound* **34**

IR: ($CHCl_3$) ν 3 051, 2 948, 1 650, 1 466, 1 377, 1 181, 1 164, 1 114, 1 025, 916.

^1H NMR: ($CDCl_3$, 200 MHz) δ 0.10 (s, 18H, $6CH_3$, $2Si(CH_3)_3$), 0.72–2.07 (m, 5H, H-4, H_2-6, H_2-7), 0.89 (s, 3H, CH_3), 0.99 (s, 3H, CH_3), 1.02 (s, 3H, CH_3), 1.12 (d, J = 6.0 Hz, 3H, CH_3), 2.2 (m, 1H, H-1′), 3.65 (m, 4H, H_2-1″, H_2-2′), 3.60 (broad s, 1H, H-7a), 6.10 (s, 1H, H-2).

^{13}C NMR: ($CDCl_3$, 50.3 MHz) δ 0.02 ($6CH_3$, $2Si(CH_3)_3$), 19.8 (CH_3), 22.8 (C-6), 25.3 (CH_3), 27.9 (CH_3), 28.7 (C-1′), 32.7 (CH_3), 32.8 (C-5), 33.1 (C-7), 48.0 (C-3a), 53.5 (C-4), 61.1 and 62.5 (C-1″, C-2′), 89.2 (C-7a), 125.5 (C-3), 140.3 (C-2).

MS: (CI, NH_3) m/z 416 ($MH^+ + NH_3$), 399 (MH^+).

[3(1R),3aR*,4R*,7aR*]-3-[(1R*)-1-Formylethyl]-3a,5,5-trimethyl-3a,4,5,6,7,7a-hexahydrobenzofuran-4-carbaldehyde* **6** *and (3R*,6aR*S*,9aR*,9bR*)-3,7,7,9b-tetramethyl-6a,7,8,9,9a,9b-hexahydro-3H-furo-[4,3,2-ef][2]benzoxepin-6(4H)-one* **35**

• *Procedure A (entry 4)*

To a solution of the Dess–Martin reagent (1.7 g, 6.0 mmol, 3 equiv) in CH_2Cl_2 (15 mL) was added *tert*-BuOH (390 µL, 6.0 mmol, 3 equiv). The reaction mixture was stirred at 20 °C for 45 min and treated with a solution of diol **31** (500 mg, 2.0 mmol) and pyridine (1.6 mL, 12 mmol, 6 equiv) in CH_2Cl_2 (5 mL). The resulting solution was stirred at this temperature for 1 h, then partitioned between a saturated aqueous Na_2SO_3 solution (30 mL) and diethyl ether (75 mL) and the phases were separated. The aqueous phase was extracted with diethyl ether (3 × 50 mL) and the combined organic phases were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. Purification by flash chromatography on silica gel gave dialdehyde **6** (50 mg, 20% yield) and lactone **35** (320 mg, 65% yield).

• *Procedure B (entry 7)*

To a solution of IBX (590 mg, 2.0 mmol, 12 equiv) in DMSO (2 mL) and pyridine (1 mL) was added at 20 °C a solution of diol **31** (44 mg, 0.17 mmol) in DMSO (2.5 mL). The resulting solution was stirred at this temperature for 1 h, then partitioned between a saturated aqueous Na_2SO_3 solution (15 mL) and diethyl ether (50 mL). The aqueous phase was extracted with diethyl ether (3 × 25 mL) and the combined organic phases were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. Purification by flash chromatography on silica gel gave dialdehyde **6** (7 mg, 15% yield), lactone **29** (22 mg, 51% yield) and lactone **35** (8 mg, 19% yield).

• *Procedure C (entry 8)*

To a solution of diol **31** (50 mg, 0.2 mmol) in CH_2Cl_2 (2 mL) at 20 °C was added TPAP (7 mg, 0.02 mmol, 0.1 equiv), 4-methylmorpholine 4-oxide (NMO) (81 mg, 0.6 mmol, 3 equiv) and molecular sieves (4 Å, 500 mg). The reaction mixture was stirred at this temperature for 3 h. The reaction mixture was then partitioned between a saturated aqueous Na_2SO_3 solution (15 mL) and diethyl ether (50 mL). The aqueous phase was extracted with diethyl ether (3 × 25 mL) and the combined organic phases were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. Purification by flash chromatography on silica gel gave dialdehyde **6** (5 mg, 10% yield) and lactone **29** (23 mg, 47% yield).

• *Procedure D (entry 9)*

To a solution of diol **31** (46 mg, 0.2 mmol) in CH_2Cl_2/THF (1:1, 7 mL) at 20 °C was added Grieco's reagent [19] (230 mg, 0.6 mmol, 3 equiv) in CH_2Cl_2/pyridine/THF (720 µL/1 mL/1 mL). The mixture was stirred in the dark at this temperature for 3 h, then partitioned between a saturated aqueous Na_2SO_3 solution (15 mL) and diethyl ether (50 mL). The aqueous phase was extracted with diethyl ether (3 × 25 mL) and the combined organic phases were

washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. No product could be isolated but compounds **36** and **37** were identified using ^1H NMR analysis.

• *Compound 6*

^1H NMR ($CDCl_3$, 200 MHz) δ 0.89–2.01 (m, 4H, H_2-6, H_2-7), 0.97 (s, 3H, CH_3), 1.15 (d, J = 6.9 Hz, 3H, CH_3, CH_3-1′), 1.23 (s, 3H, CH_3), 1.34 (s, 3H, CH_3), 2.08 (d, J = 4.5 Hz, 1H, H-4), 2.92 (q, J = 6.9 Hz, 1H, H-1′), 3.95 (t, J = 3.4 Hz, 1H, H-7a), 6.09 (s, 1H, H-2), 9.51 (s, 1H, H-2′), 9.90 (d, J = 4.5 Hz, 1H, H-1″).

• *Compound 35*

IR (CCl_4) ν 2 960, 2 930, 1 710, 1 625, 1 450, 1 250, 1 135, 1 090, 850.

^1H NMR ($CDCl_3$, 200 MHz) δ 0.72–2.10 (m, 4H, H_2-9, H_2-8), 1.00 (s, 3H, CH_3), 1.08 (d, J = 6.9 Hz, 3H, CH_3, CH_3-3), 1.20 (s, 3H, CH_3), 1.30 (s, 3H, CH_3), 2.40 (s, 1H, H-6a), 2.66 (qdd, J = 6.9, 11.1, 2.6 Hz, 1H, H-3), 3.82 (d, J = 11.1 Hz, 1H, Ha-4), 4.07 (dd, J = 11.1, 2.6 Hz, 1H, Hb-4), 4.13 (t, J = 3.1 Hz, 1H, H-9a), 6.07 (s, 1H, H-2).

^{13}C NMR: ($CDCl_3$, 50.3 MHz) δ 16.2 (CH_3), 22.5 (CH_3), 23.5 (C-8), 23.8 (CH_3), 29.7 (C-3), 29.5 (CH_3), 30.7 (C-7), 33.4 (C-9), 47.5 (C-9b), 50.0 (C-6a), 66.1 (C-8), 88.3 (C-9a), 112.0 (C-2), 141.8 (C-2a), 172.3 (C-6).

MS: (Cl, NH_3) m/z 268 ($MH^+ + NH_3$), 251 (MH^+).

Anal calc for $C_{15}H_{22}O_3$, 250.33: C, 71.97; H, 8.86. Found; C, 71.92; H, 8.92.

[3(1R),3aR*,4R*,7aR*]-4-{[(tert-Butyldimethylsilyl)-oxy]methyl}-3a,5,5-trimethyl-3-(1-methylallyl)-3a,4,5,6,7,7a-hexahydrobenzofuran* **38**

To a solution of PPh_3CH_3Br (320 mg, 0.91 mmol, 3 equiv) in THF (2 mL) cooled at 0 °C was added a 1.5M *n*-BuLi solution in hexane (540 μL, 0.80 mmol, 2.7 equiv) and the resulting solution was stirred at this temperature for 30 min. A solution of aldehyde **32** (100 mg, 0.3 mmol) in THF (1 mL) was transferred via cannula to the above solution and the reaction allowed to warm to 20 °C and stirred for 12 h at this temperature and partitioned between water (10 mL) and diethyl ether (50 mL) and the phases were separated. The aqueous phase was extracted with diethyl ether (3 × 25 mL) and the combined organic phases were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. Purification by flash chromatography on silica gel gave compound **38** (73 mg, 67% yield).

IR: ($CHCl_3$) ν 3 013, 2 952, 1 578, 1 434, 1 158, 1 018, 968, 843.

^1H NMR ($CDCl_3$, 200 MHz) δ 0.08 and 0.10 (2s, 6H, $2CH_3$, $Si(CH_3)_2$), 0.95–1.90 (m, 5H, H_2-6, H_2-7, H-4), 0.90 (3s, 9H, $3CH_3$, $SiC(CH_3)_3$), 1.05 (2s, 6H, $2CH_3$), 1.17 (s, 3H, CH_3), 1.17 (d, J = 7.8 Hz, 3H, CH_3, CH_3-2), 2.90 (m, 1H, H-1′), 3.78 (dd, J = 11.1, 7.3 Hz, 1H, Ha-1″), 3.84 (dd, J = 11.1, 3.4 Hz, 1H, Hb-1″), 3.9 (t, J = 3.6 Hz, 1H, H-7a), 4.9-5.1 (m, 2H, H-3′), 5.9 (m, 1H, H-2′), 6.05 (s, 1H, H-2).

MS: (Cl, NH_3) m/z 382 ($MH^+ + NH_3$), 365 (MH^+).

Anal calc for $C_{22}H_{40}O_2Si$ 364.60: C, 72.27; H, 11.03. Found; C, 72.39; H, 10.91.

[3aR,4R*,7aR*)-3a,5,5-Trimethyl-3-[(1R*)-1-methylallyl]-3a,4,5,6,7,7a-hexahydrobenzofuran-4-carbaldehyde* **39**

To a solution of silyl derivative **38** (130 mg, 0.35 mmol) in acetonitrile (950 μL) at 20 °C was added a 48% aqueous HF solution (50 μL). The resulting cloudy mixture was stirred at 20 °C for 1 h, and the reaction quenched with saturated aqueous $NaHCO_3$ solution (5 mL) and diluted with diethyl ether (30 mL). The phases were separated and the aqueous phase was extracted with diethyl ether (3 × 25 mL). The combined organic phases were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. Purification by flash chromatography on silica gel gave the desired alcohol which was carried onto the next step without further purification.

To a solution of the above alcohol in dichloromethane (1 mL) was added the Dess–Martin reagent (200 mg, 0.7 mmol, 2 equiv) and the reaction mixture was stirred at 20 °C for 1.5 h, then partitioned between a saturated aqueous Na_2SO_3 solution (5 mL) and diethyl ether (30 mL) and the phases were separated. The aqueous phase was extracted with diethyl ether (3 × 25 mL) and the combined organic phases were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. Purification by flash chromatography on silica gel gave aldehyde **39** (65 mg, 67% yield).

IR ($CHCl_3$) ν 3 006, 2 984, 1 712, 1 578, 1 445, 1 151, 1 021, 998, 851.

^1H NMR ($CDCl_3$, 400 MHz) δ 0.84–2.05 (m, 4H, H_2-6′, H_2-7′), 0.95 (s, 3H, CH_3), 1.12 (s, 3H, CH_3), 1.12 (d, J = 3.5 Hz, 3H, CH_3-1″), 1.38 (s, 3H, CH_3), 2.14 (d, J = 4.2 Hz, 1H, H-4′), 2.65 (dq, J = 3.5, 4.0 Hz, 1H, H-1″), 3.92 (t, J = 3.6 Hz, 1H, H-7′a), 4.95 (d, J = 16.5 Hz, 1H, Ha-3″), 4.98 (d, J = 10.5 Hz, 1H, Hb-3″), 5.84 (ddd, J = 16.5, 10.5, 4.0 Hz, 1H, H-2′), 6.09 (s, 1H, H-2′), 9.92 (d, J = 4.2 Hz, 1H, H-1).

MS: (Cl, NH_3) m/z 294 ($MH^+ + NH_3$), 277 (MH^+).

(3R,4S*,5R*,5aR*,8aR*,8bR*)-3,6,6,8b-Tetramethyl-4,5,5a,6,7,8,8a,8b-octahydronaphtho[1,8-bc]furan-4,5-diol* **41**

To a 0.1 M SmI_2 [31] solution in THF (28 mL, 2.8 mmol, 2.5 equiv) cooled to −78 °C was added a solution of the mixture of dialdehyde **6** (60 mg, 0.2 mmol) and lactone **35** (220 mg, 0.9 mmol) and *t*-BuOH (210 μL, 2.8 mmol, 2.5 equiv) in THF (22 mL). The resulting solution was stirred at this temperature for 1 h and allowed to warm to 20 °C over 2 h. The reaction was then quenched with a saturated aqueous $NaHCO_3$ solution (30 mL) and the phases separated. The aqueous phase was extracted with ethyl acetate (3 × 75 mL) and the combined organic phases were washed with a saturated aqueous Na_2SO_3 solution (3 × 25 mL), then brine, dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. Purification by flash chromatography on silica gel gave diol **41** (54 mg, 95% yield) and recovered lactone **35** (220 mg, 99%).

IR: ($CHCl_3$) ν 3 356, 2 947, 1 614, 1 451, 1 378, 1 334, 978.

^1H NMR: ($CDCl_3$, 200 MHz, NOE experiments, forskolin numbering) δ 0.97 (s, 3H, CH_3), 1.00–1.83 (m, 4H, Ha-2, H_2-3, OH), 1.18 (s, 3H, CH_3), 1.18 (d, J = 6.9 Hz, 3H, CH_3, CH_3-8), 1.50 (s, 3H, CH_3), 2.02 (m, 1H, Hb-2), 2.17 (d, J = 2.5 Hz, 1H, H-5), 2.22 (d, J = 7.3 Hz, 1H, OH), 2.50 (qdd, J = 6.3, 9.6, 1.8 Hz, 1H, H-8), 3.01 (ddd, J = 9.6, 7.3, 3.1 Hz, 1H, H-7), 4.18 (dd, J = 9.0, 7.1 Hz, 1H, H-1), 4.24 (dd, J = 3.1, 2.6 Hz, 1H, H-6), 5.90 (d, J = 1.8 Hz, 1H, H-11).

^{13}C NMR: ($CDCl_3$, 50.3 MHz, forskolin numbering) δ 14.3 (CH_3-8), 24.8 (C-3), 26.1 (CH_3), 27.3 (CH_3), 30.3 (CH_3), 30.9 (C-8), 31.4 (C-4), 34.5 (C-2), 47.7 (C-10), 50.5 (C-5), 71.4 (C-7), 80.4 (C-6), 90.3 (C-1), 125.1 (C-9), 136.5 (C-11).

MS: (CI, NH_3) m/z 270 ($MH^+ + NH_3$), 253 (MH^+), 235, 217.

Anal calc for $C_{15}H_{24}O_3$, 252.34: C, 71.39; H, 9.59. Found; C, 71.49; H, 9.46.

RX analysis of ***41***

Lists of coordinates, distances, angles and anisotropic thermal factors can be found in tables II-VI. Compound **41** was studied by X-ray crystallography. Space group: $P21/n$; parameters: a = 20.578(5) Å; b = 8.009(3) Å; c = 8.247(3) Å; β = 99.9(1)°; Z = 4.

Table II. Positional parameters ($\times 10^4$) and mean recalculated isotropic factors ($\times 10^3$) for non-hydrogen atoms[a].

Atom	*x*	*y*	*z*	$< U >$
C1	8794 (3)	465 (7)	599 (7)	40 (6)
C2	9226 (3)	536 (8)	2285 (8)	50 (7)
C3	9704 (3)	−928 (9)	2440 (8)	49 (7)
C4	9351 (3)	−2612 (7)	2581 (6)	37 (5)
C18	9762 (3)	−4004 (10)	1980 (10)	60 (8)
C19	9324 (3)	−2919 (10)	4406 (7)	55 (7)
C5	8641 (3)	−2481 (7)	1615 (6)	33 (5)
C6	8238 (3)	−4102 (7)	1251 (6)	36 (5)
C7	7505 (3)	−3725 (7)	708 (7)	38 (6)
C8	7365 (3)	−2513 (8)	−742 (6)	37 (5)
C17	6628 (3)	−2028 (10)	−1119 (8)	52 (7)
C9	7810 (3)	−1026 (7)	−365 (6)	32 (5)
C10	8543 (3)	−1310 (7)	91 (6)	34 (5)
C11	7674 (3)	519 (8)	−59 (7)	41 (6)
C20	8849 (3)	−1939 (8)	−1378 (7)	47 (7)
O1	8214 (2)	1511 (5)	550 (5)	51 (4)
O6	8470 (2)	−5100 (5)	30 (5)	46 (4)
O7	7150 (2)	−5246 (6)	324 (6)	56 (5)

[a] Given in Å^2 and calculated as

$$< U >= \frac{1}{3} \sum_i \sum_j U_{ij} \cdot a_i^* \cdot a_j^* \cdot \mathbf{a}_i \cdot \mathbf{a}_j.$$

Table III. Positional parameters ($\times 10^3$) and mean recalculated isotropic factors ($\times 10^3$) for hydrogen atoms.

Atom	*x*	*y*	*z*	*U*
H1	909	89	−24	68
H2	950	158	241	57
H2	892	57	316	31
H3	992	−88	144	59
H3	1007	−81	348	22
H18	973	−385	75	128
H18	958	−519	218	108
H18	1021	−391	262	63
H19	902	−201	471	105
H19	975	−307	516	53
H19	907	−407	440	83
H5	840	−184	238	31
H6	833	−470	238	23
H7	735	−315	166	100
H8	747	−319	−173	21
H17	655	−120	−206	82
H17	652	−146	−9	97
H17	640	−313	−134	80
H11	729	120	−14	50
H20	935	−210	−103	46
H20	870	−117	−230	56
H20	869	−313	−175	72
H-O7	744	−582	−35	161
H-O6	842	353	35	50

(3aR,6R*,6aS*,9aR*,9bR*,9cR*)-1,1,6,8,8,9c-Hexamethyl-2,3,3a,6,6a,9a,9b,9c-octahydro-1H-furo[4',3',2':4,5]naphtho[1,2-d][1,3]dioxole* ***42***

A solution of diol **41** (50 mg, 0.2 mmol) and pyridinium toluenesulfinate (PPTS) (5 mg, 0.02 mmol, 0.1 equiv) in 2-methoxypropene (1 mL) at 20 °C was stirred for 12 h. The resulting solution was then partitioned between water (5 mL) and diethyl ether (25 mL) and the phases were separated. The aqueous phase was extracted with diethyl ether (3 × 25 mL) and the combined organic phases were dried over $MgSO_4$, filtered and concentrated in vacuo. The resulting oil was purified by flash chromatography on silica gel to give the title product **42** (55 mg, 95% yield).

Table IV. Anisotropic thermal parameters ($\times 10^4$) for non-hydrogen atoms.

Atom	*U11*	*U22*	*U33*	*U23*	*U13*	*U12*
C1 4	29 (36)	264 (34)	516 (36)	26 (30)	150 (28)	−26 (28)
C2 5	36 (42)	320 (39)	638 (42)	−48 (33)	73 (34)	−108 (33)
C3 4	19 (38)	530 (45)	522 (40)	−17 (36)	57 (31)	−91 (33)
C4 3	45 (32)	442 (38)	319 (29)	0 (28)	48 (23)	3 (28)
C18	415 (41)	630 (54)	743 (51)	−12 (41)	48 (36)	180 (37)
C19	528 (43)	771 (57)	335 (33)	101 (36)	−114 (30)	6 (41)
C5	376 (32)	338 (34)	265 (27)	−3 (26)	110 (23)	59 (26)
C6	435 (35)	390 (37)	262 (28)	30 (26)	130 (24)	10 (28)
C7	476 (36)	322 (36)	332 (31)	−16 (27)	69 (26)	−58 (29)
C8	391 (34)	494 (39)	231 (27)	−25 (28)	36 (23)	10 (30)
C17	381 (37)	669 (52)	500 (40)	2 (39)	−9 (30)	28 (36)
C9	368 (32)	404 (40)	203 (25)	17 (25)	82 (22)	−10 (27)
C10	399 (32)	389 (35)	246 (26)	39 (26)	107 (23)	−7 (28)
C11	416 (38)	434 (42)	383 (32)	27 (31)	78 (27)	−22 (33)
C20	572 (44)	523 (44)	327 (31)	14 (32)	246 (29)	27 (34)
O1	561 (28)	315 (24)	628 (27)	26 (22)	153 (22)	45 (22)
O6	564 (26)	323 (23)	478 (23)	−98 (20)	203 (19)	−9 (20)
O7	493 (28)	441 (29)	739 (31)	−1 (25)	108 (23)	−157 (23)

Table V. Distances (Å) for non-hydrogen atoms with esd's given in parentheses.

C1-C2	1.517 (9)	C6-C7	1.528 (8)
C1-C10	1.545 (8)	C6-O6	1.430 (7)
C1-O1	1.454 (7)	C7-C8	1.529 (8)
C2-C3	1.521 (9)	C7-O7	1.428 (7)
C3-C4	1.546 (9)	C8-C17	1.544 (9)
C4-C18	1.533 (9)	C8-C9	1.503 (8)
C4-C19	1.535 (8)	C9-C10	1.507 (8)
C4-C5	1.543 (8)	C9-C11	1.303 (9)
C5-C6	1.542 (8)	C10-C20	1.543 (8)
C5-C10	1.553 (7)	C11-O1	1.388 (8)

Table VI. Bond angles (°) for non-hydrogen atoms with esd's given in parentheses.

C2-C1-C10	113.5 (5)	C5-C6-C7	111.2 (4)
C2-C1-O1	110.6 (5)	C5-C6-O6	112.0 (4)
C10-C1-O1	106.7 (4)	C7-C6-O6	109.6 (4)
C1-C2-C3	108.4 (5)	C6-C7-C8	113.4 (5)
C2-C3-C4	111.9 (5)	C6-C7-O7	109.8 (5)
C3-C4-C18	108.5 (5)	C8-C7-O7	110.4 (5)
C3-C4-C19	108.1 (5)	C7-C8-C17	111.3 (5)
C3-C4-C5	108.5 (5)	C7-C8-C9	108.4 (5)
C18-C4-C19	108.4 (5)	C17-C8-C9	112.6 (5)
C18-C4-C5	114.2 (5)	C8-C9-C10	118.7 (5)
C19-C4-C5	109.1 (5)	C8-C9-C11	130.5 (5)
C4-C5-C6	118.2 (4)	C10-C9-C11	109.6 (5)
C4-C5-C10	116.0 (4)	C1-C10-C5	110.2 (4)
C6-C5-C10	111.1 (4)	C1-C10-C9	101.7 (4)
C1-C10-C12	110.5 (5)	C9-C10-C20	112.3 (5)
C9-C11-O1	115.3 (5)	C5-C10-C9	106.1 (4)
C1-O1-C11	106.4 (4)	C5-C10-C20	115.1 (5)

IR: ($CHCl_3$) ν 2 021, 1 831, 1 621, 1 469, 1 354, 1 211, 891.

^1H NMR: ($CDCl_3$, 200 MHz, forskolin numbering) δ 1.01 (s, 3H, CH_3), 1.11 (s, 3H, CH_3), 1.13 (d, J = 6.7 Hz, 3H, CH_3-8), 1.36 (s, 3H, CH_3), 1.47 (s, 3H, CH_3), 1.53 (s, 3H, CH_3), 1.36–1.66 (m, 4H), 2.0 (m, 1H), 2.45 (qdd, J = 6.7, 8.2, 1.8, Hz, 1H, H-8), 3.42 (dd, J = 8.2, 4.7 Hz, 1H, H-7), 4.16 (t, J = 7.5 Hz, 1H, H-1), 4.40 (dd, J = 4.7, 2.6 Hz, 1H, H-6), 5.84 (d, J = 1.8 Hz, 1H, H-11).

^{13}C NMR: ($CDCl_3$, 50.3 MHz, forskolin numbering) δ 15.3 (CH_3-8), 24.5 (C-3), 24.7 (CH_3), 26.2 (CH_3), 26.8 (CH_3), 28.9 (CH_3), 30.2 (CH_3), 31.6 (C-4), 32.4 (C-8), 35.1 (C-2), 47.7 (C-10), 49.2 (C-5), 75.3 (C-7), 84.5 (C-6), 89.2 (C-1), 109.5 (C, O-C(CH_3)$_2$-O), 125.7 (C-9), 136.2 (C-11).

MS: (CI, NH_3) m/z 293 (MH^+), 235, 217.

Anal calc for $C_{18}H_{28}O_3$, 292.40: C, 73.93; H, 9.63. Found; C, 73.89; H, 9.59.

(3aR,5aS*,6R*,6aR*,9aR*,9bR*,9cR*)-1,1,6,8,8,9c-Hexamethyl-decahydro-5H-furo-[4',3',2':4,5]naphtho[1,2-d][1,3]dioxol-5-one* **43** *and (3aR*,4R*,5aR*,6S*,9aS*,9bS*)-6-formyloxy-2,2,4,5a,9,9-hexamethyl-octahydronaphtho-[1,2-d][1,3]dioxol-5(4H)-one* **44**

• *Procedure A*

To a solution of compound **42** (30 mg, 0.1 mmol) in dichloromethane (1 mL) at 20 °C was added PCC (35 mg, 0.15 mmol, 1.5 equiv). The reaction mixture was stirred at this temperature for 3 h and partitioned between water (10 mL) and diethyl ether (40 mL). The aqueous phase was extracted with diethyl ether (3 × 25 mL) and the combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The resulting oil was purified by flash chromatography to give lactone **43** (13 mg, 43% yield) and formyl ketal **44** (14 mg, 43% yield).

• *Procedure B*

A solution of compound **42** (30 mg, 0.1 mmol) in dichloromethane (4.5 mL) and methanol (0.5 mL) at −78 °C was treated with a stream of ozone until it turned blue. Oxygen was then bubbled through the solution till the blue color disappeared. Argon was then bubbled through the same solution and Me_2S (75 μL, 1 mmol, 10 equiv) was added at −78 °C and the resulting mixture allowed to warm up to 20 °C and stirred at 20 °C for 12 h. The solvent was then removed in vacuo and the residue purified by flash chromatography on silica gel to give the desired formyl ketal 44 (32 mg, 95% yield).

• *Procedure C*

To a solution of **41** (58 mg, 0.2 mmol) in MeOH (1 mL) at 25 °C was added $15H^+$ Amberlist resin (50 mg). The reaction mixture was stirred at this temperature for 12 h and partitioned between a saturated aqueous NaCl solution (5 mL) and diethyl ether (25 mL) and the phases were separated. The aqueous phase was extracted with 3 × 25 mL of diethyl ether and the combined organic phases were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo to give (2R*/S*,2aR*,3S*,4R*,5S*,5aS*,8aS*,8bS*)-2-methoxy-3,6,6,8b-tetramethyldecahydronaphtho[1,8-*bc*]furan-4,5-diol (55 mg, 96% yield) which was carried on to the next step without further purification.

IR ($CHCl_3$): 3 343, 2 951, 1 451, 1 354, 1 314, 991, 878.

^1H NMR: ($CDCl_3$, 200 MHz) δ 0.97 (s, 3H, CH_3), 1.01–1.83 (m, 7H, H-5, H_2-2, H_2-3, H-9, OH), 1.09 (d, J = 6.9 Hz, 3H, CH_3, CH_3-8), 1.18 (s, 3H, CH_3), 1.35 (s, 3H, CH_3), 2.1 (m, 1H, H-8), 2.3 (m, 1H, OH), 3.28 (dd, J = 9.5, 4.5 Hz, 1H, H-7), 3.4 (s, 3H, CH_3, OCH_3), 3.75 (t, J = 3.6 Hz, 1H, H-1), 4.25 (dd, J = 4.5, 2.6 Hz, 1H, H-1), 4.8 (d, J = 6.2 Hz, 1H, H-11).

MS: (CI, NH_3) 302 (MH^+ + NH_3), 285 (MH^+), 284.

A solution of the preceding diol (55 mg, 0.2 mmol) and PPTS (5 mg, 0.02 mmol, 0.1 equiv) in 2-methoxypropene (1 mL) at 20 °C was stirred for 3 h. The resulting solution was then partitioned between a saturated aqueous NaCl solution (5 mL) and diethyl ether (25 mL) and the phases were separated. The aqueous phase was extracted with diethyl ether (3 × 25 mL) and the combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The resulting oil was purified by flash chromatography on silica gel to give protected diol (3aR*,5R*/S*,5aS*,6R*,6aS*,9aR*,9bR*,9cR*)-1,1,6,8,8,9c-hexamethyl-5-methoxydecahydro-5H-furo[4',3',2':4,5]naphtho[1,2-*d*][1,3]dioxole (59 mg, 95% yield).

IR: ($CHCl_3$) 2 962, 1 451, 1 354, 1 305, 978, 792.

^1H NMR ($CDCl_3$, 200 MHz, forskolin numbering) δ 1.00 (s, 3H, CH_3), 1.07 (d, J = 7.1 Hz, 3H, CH_3-8), 1.11 (s, 3H, CH_3), 1.33 (s, 3H, CH_3), 1.36 (s, 3H, CH_3), 1.51 (s, 3H, CH_3), 1.45 (m, 4H, H-2, H-3), 1.48 (d, J = 2.1, 1H, H-5), 1.71 (t, J = 6.6 Hz, 1H, H-9), 1.99 (qdd, J = 7.1, 9.3, 6.6 Hz, 1H, H-8), 3.43 (s, 3H, CH_3, OCH_3), 3.65 (dd, J = 9.3, 5.1 Hz, 1H, H-7), 3.78 (t, J = 2.8 Hz, 1H, H-1), 4.46 (dd, J = 5.1, 2.1 Hz, 1H, H-6), 4.74 (d, J = 6.6 Hz, 1H, H-11).

^{13}C NMR: ($CDCl_3$, 50.3 MHz, forskolin numbering) δ 16.8 (CH_3-8), 19.9 (CH_3), 22.2 (C-3), 23.3 (CH_3), 26.5 (CH_3),

28.9 (CH_3), 31.3 (CH_3), 32.2 (C-8), 33.3 (C-4), 37.0 (C-2), 41.2 (C-10), 43.5 (C-9), 56.1 (C-5), 62.3 (CH_3, OCH_3), 73.8 (C-7), 81.7 (C-6), 83.5 (C-1), 105.9 (C-11), 109.9 (C, $OC(CH_3)_2O$).

MS: (CI, NH_3) 342 ($MH^+ + NH_3$), 325 (MH^+).

To a solution of this compound (6 mg, 0.02 mmol) in dichloromethane (0.5 mL) cooled to 0 °C was added *m*-CPBA (5 mg, 0.03 mmol, 1.5 equiv), followed by $BF_3{\cdot}OEt_2$ (10 μL, 0.08 mmol, 4 equiv). The reaction mixture was allowed to warm to 20 °C with stirring for 3 h and then partitioned between water (10 mL) and diethyl ether (25 mL). The aqueous phase was extracted with diethyl ether (3 × 25 mL) and the combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The resulting oil was purified by flash chromatography to give lactone **43** (4 mg, 70% yield).

• *Procedure D*

To a solution of the Dess–Martin reagent (325 mg, 1.2 mmol, 1.5 equiv) in CH_2Cl_2 (3 mL) was added a solution of diol **49** (see below, 25 mg, 0.8 mmol) in CH_2Cl_2 (5 mL). The resulting solution was stirred at 20 °C for 1 h, then partitioned between a saturated aqueous Na_2SO_3 solution (10 mL) and diethyl ether (40 mL). The aqueous phase was extracted with diethyl ether (3 × 25 mL) and the combined organic phases were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. Purification by flash chromatography on silica gel gave formyl ketal **44** (23 mg, 92% yield).

• *Compound 43*

IR: ($CHCl_3$) ν 3 021, 2 978, 1 683, 1 431, 1 341, 1 315, 958, 787.

^1H NMR: ($CDCl_3$, 200 MHz, forskolin numbering) δ 1.03 (s, 3H, CH_3), 1.14 (s, 3H, CH_3), 1.35 (s, 3H, CH_3), 1.40 (d, J = 7.1 Hz, 3H, CH_3-8), 1.49 (s, 3H, CH_3), 1.51 (s, 3H, CH_3), 1.30–1.82 (m, 5H, H_2-2, H_2-3, H-5), 1.98 (qdd, J = 7.1, 9.5, 5.8 Hz, 1H, H-8), 2.32 (d, J = 5.8 Hz, 1H, H-9), 3.78 (dd, J = 9.5, 4.9 Hz, 1H, H-7), 4.06 (t, J = 3.2 Hz, 1H, H-1), 4.47 (dd, J = 4.9, 2.2 Hz, 1H, H-6).

^{13}C NMR: ($CDCl_3$, 50.3 MHz, forskolin numbering) δ 14.7 (CH_3-8), 19.7 (CH_3), 21.8 (C-3), 23.0 (CH_3), 26.4 (CH_3), 29.0 (CH_3), 31.3 (CH_3), 31.6 (C-8), 33.0 (C-4), 36.5 (C-2), 42.4 (C-10), 43.7 (C-9), 57.8 (C-5), 73.5 (C-7), 80.5 (C-6), 83.6 (C-1), 110.2 (C, $OC(CH_3)_2O$), 176.3 (C-11).

MS: (CI, NH_3) m/z 326 ($MH^+ + NH_3$), 309 (MH^+).

Anal calc for $C_{18}H_{28}O_4$, 308.40: C, 70.10; H, 9.15. Found: C, 70.19; H, 9.01.

• *Compound 44*

IR: (NaCl) ν 2 990, 2 925, 1 725, 1 715, 1 385, 1 275, 1 105, 855.

^1H NMR: ($CDCl_3$, 200 MHz, forskolin numbering) δ 1.16 (d, J = 7.1 Hz, 3H, CH_3-8), 1.23 (s, 3H, CH_3), 1.27 (s, 3H, CH_3), 1.38 (s, 3H, CH_3), 1.46 (s, 3H, CH_3), 1.52 (s, 3H, CH_3), 1.30–1.89 (m, 4H, H_2-2, H_2-3), 2.05 (d, J = 2.9 Hz, 1H, H-5), 2.75 (qd, J = 7.1, 6.2 Hz, 1H, H-8), 3.99 (t, J = 6.2 Hz, 1H, H-7), 4.67 (dd, J = 6.2, 2.9 Hz, 1H, H-6), 5.16 (broad s, 1H, H-1), 7.99 (s, 1H, CHO).

^{13}C NMR: ($CDCl_3$, 50.3 MHz, forskolin numbering) δ 13.5 (CH_3-8), 21.0 (CH_3), 22.8 (C-3), 24.0 (CH_3), 24.5 (CH_3), 27.3 (CH_3), 32.4 (CH_3), 34.5 (C-4), 36.3 (C-2), 42.7 (C-8), 44.9 (C-5), 50.1 (C-10), 72.1 (C-7), 80.0 (C-6), 74.8 (C-1), 108.6 (C, $OC(CH_3)_2O$), 159.9 (C=O, CHO), 212.1 (C=O, C-9).

MS: (CI, NH_3) m/z 342 ($MH^+ + NH_3$), 325 (MH^+).

(3aR,5R*/S*,5aR*,6S*,6aS*,9aR*,9bR*,9cS*)-5-[(3-Chlorobenzoyl)oxy]-1,1,6,8,8,9c-hexamethyldecahydro-1H-furo[4',3',2':4,5]naphtho-[1,2-d][1,3]dioxol-5a-ol 47*

To a solution of **42** (55 mg, 0.19 mmol) in dichloromethane (5 mL) cooled to 0 °C was added *m*-CPBA (110 mg, 0.3 mmol, 1.5 equiv). The resulting solution was allowed to warm up to 20 °C, stirred at this temperature for 1 h and partitioned between a saturated aqueous $NaHCO_3$ solution (5 mL) and diethyl ether (75 mL). The phases were separated and the aqueous phase was extracted with diethyl ether (3 × 50 mL) and the combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo. Purification by flash chromatography gave **47** (74 mg, 85% yield).

IR ($CHCl_3$) ν 3 451, 3 001, 2 995, 1 658, 1 644, 1 421, 1 078, 935, 865, 745.

^1H NMR: ($CDCl_3$, 200 MHz, forskolin numbering) δ 1.03 (d, J = 7.1 Hz, 3H, CH_3-8), 1.07 (s, 3H, CH_3), 1.21 (s, 3H, CH_3), 1.37 (s, 3H, CH_3), 1.38 (s, 3H, CH_3), 1.53 (s, 3H, CH_3), 1.00–2.10 (m, 6H, H_2-2, H_2-3, H-4, H-8), 2.90 (s, 1H, OH), 3.72 (dd, J = 9.2, 4.9 Hz, 1H, H-7), 4.35 (t, J = 2.6 Hz, 1H, H-1), 4.50 (dd, J = 4.9, 2.3 Hz, 1H, H-6), 6.41 (s, 1H, H-11), 7.43 (t, J = 7.9 Hz, 1H, Ar-H), 7.58 (dd, J = 7.9, 1.0 Hz, 1H, Ar-H), 7.92 (d, J = 7.9 Hz, 1H, Ar-H), 8.00 (d, J = 1.0 Hz, 1H, Ar-H).

MS: (CI, NH_3) m/z 466 (MH^+), 465.

(3aR,5R*/S*,5aR*,6S*,6aS*,9aR*,9bR*,9cS*)-1,1,6,8,8,9c-Hexamethyl-5-methoxydecahydro-1H-furo[4',3',2':4,5]naphtho[1,2-d][1,3]dioxol-5a-ol 48*

To a solution of diol **41** (80 mg, 0.3 mmol) in dichloromethane (5 mL) cooled at 0 °C was added *m*-CPBA (190 mg, 0.5 mmol, 1.5 equiv). The resulting solution was allowed to warm to 20 °C with stirring at this temperature for 1 h and partitioned between a saturated aqueous $NaHCO_3$ solution (5 mL) and diethyl ether (75 mL). The phases were separated and the aqueous phase was extracted with diethyl ether (3 × 50 mL) and the combined organic phases washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The resulting oil was diluted at 20 °C with THF/1 N HCl solution (2 mL, 1:1), stirred at this temperature for 1 h and partitioned between water (5 mL) and diethyl ether (50 mL). The phases were separated, the aqueous phase was extracted with diethyl ether (3 × 50 mL) and the combined organic phases were washed with brine, then dried over $MgSO_4$, filtered and concentrated in vacuo. Purification by flash chromatography gave (2R*/S*,2aS*,3R*,4R*,5S*,5aS*,8aS*,8bR*)-3,6,6,8b-tetramethyldecahydronaphtho[1,8-*bc*]furan-2,2a,4,5-tetraol (62 mg, 68% yield).

IR: ($CHCl_3$) ν 3 455, 3 051, 2 987, 1 831, 1 421, 1 081, 945, 843.

^1H NMR ($CDCl_3$, 200 MHz, forskolin numbering) δ 1.02 (s, 3H, CH_3), 1.09 (s, 3H, CH_3), 1.24 (d, J = 6.9 Hz, 3H, CH_3-8), 1.41 (s, 3H, CH_3), 1.00–2.21 (m, 10H, H_2-2, H_2-3, H-5, H-8, OH-4), 3.35 (dd, J = 9.5, 4.9 Hz, 1H, H-7), 4.30 (t, J = 1.6 Hz, 1H, H-1), 4.30 (dd, J = 4.9, 2.2 Hz, 1H, H-6), 5.30 (s, 1H, H-11).

^{13}C NMR: ($CDCl_3$, 50.3 MHz, forskolin numbering) δ 11.3 (CH_3-8), 14.0 (CH_3), 21.6 (C-3), 23.7 (CH_3), 32.7 (CH_3), 33.4 (C-4), 36.2 (C-2), 37.7 (C-8), 48.0 (C-10), 45.3 (C-5), 69.4 (C-7), 75.2 (C-1), 83.7 (C-9), 84.9 (C-6), 98.1 (C-11).

MS: (CI, NH_3) m/z 304 ($MH^+ + NH_3$), 287 (MH^+), 180, 162.

To a solution of the above tetraol (41 mg, 0.14 mmol) in MeOH (1 mL) at 20 °C was added $15H^+$ amberlist resin (40 mg). The reaction mixture was stirred at this temperature for 12 h and partitioned between a saturated aqueous NaCl solution (5 mL) and diethyl ether (25 mL) and the phases were separated. The aqueous phase was extracted with diethyl ether (3 × 25 mL) and the combined organic phases were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo to give (*2R*/S**,2aS*,3R*,4R*,5S*,5aS*,8aS*,8bR**)-2-methoxy-3,6,6,8b-tetramethyldecahydronaphtho[1,8-*bc*]furan-2a,4,5-triol (36 mg, 85% yield) which was carried on to the next step without further purification.

IR: ($CHCl_3$) ν 3 445, 3 021, 2 997, 1 421, 1 078, 935, 865.

^1H NMR ($CDCl_3$, 200 MHz, forskolin numbering) δ 0.99 (s, 3H, CH_3), 1.07 (d, J = 6.9 Hz, 3H, CH_3-8), 1.21 (s, 3H, CH_3), 1.31 (s, 3H, CH_3), 1.01–1.81 (m, 8H, H_2-2, H_2-3, H-5, 3OH), 1.98 (qd, J = 6.9, 9.4 Hz, 1H, H-8), 3.25 (dd, J = 9.4, 4.9 Hz, 1H, H-7), 3.53 (s, 3H, CH_3, OCH_3), 4.08 (t, J = 3.5 Hz, 1H, H-1), 4.27 (dd, J = 4.9, 2.2 Hz, 1H, H-6), 4.89 (s, 1H, H-11).

MS: (CI, NH_3) *m/z* 318 (MH^+ + NH_3), 301 (MH^+), 300.

A solution of the above triol (35 mg, 0.12 mmol) and PPTS (5 mg, 0.02 mmol, 0.15 equiv) in 2-methoxypropene (1 mL) was stirred at 20 °C for 3 h. The resulting solution was partitioned between a saturated aqueous NaCl solution (5 mL) and diethyl ether (25 mL). The aqueous phase was extracted with diethyl ether (3 × 25 mL) and the combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The resulting oil was purified by flash chromatography to give **48** (38 mg, 95% yield).

IR ($CHCl_3$) ν 3 453, 3 014, 2 967, 1 422, 1 077, 935, 865.

^1H NMR ($CDCl_3$, 200 MHz, forskolin numbering) δ 1.00 (s, 3H, CH_3), 1.01 (d, J = 7.1 Hz, 3H, CH_3-8), 1.15 (s, 3H, CH_3), 1.31 (s, 3H, CH_3), 1.35 (s, 3H, CH_3), 1.51 (s, 3H, CH_3), 1.00–2.10 (m, 6H, H_2-2, H_2-3, H-4, H-8), 3.29 (s, 1H, OH), 3.51 (s, 3H, CH_3, OCH_3), 3.65 (dd, J = 9.3, 4.9 Hz, 1H, H-7), 4.10 (t, J = 2.8 Hz, 1H, H-1), 4.42 (dd, J = 4.9, 2.3 Hz, 1H, H-6), 4.80 (s, 1H, OH), 4.80 (s, 1H, H-11).

MS: (CI, NH_3) *m/z* 346 (MH^+ + NH_3), 329 (MH^+), 328.

(3aR,5R*/S*,5aR*,6S*,6aS*,9aR*,9bR*,9cS*)-1,1,6,8,8,9c-Hexamethyl-decahydro-1H-furo[4',3',2':4,5]naphtho[1,2-b][1,3]dioxole-5,5a-diol 49*

A solution of the above tetrol (*2R*/S*,2aS*,3R*,4R*,5S*,5aS*,8aS*,8bR**)-3,6,6,8b-tetramethyldecahydronaphtho-[1,8-*bc*]furan-2,2a,4,5-tetraol prepared above (see preparation of **48**, 60 mg, 0.2 mmol) and PPTS (5 mg, 0.02 mmol, 0.1 equiv) in 2-methoxypropene (1 mL) was stirred at 20 °C for 3 h. The resulting solution was partitioned between a saturated aqueous NaCl solution (5 mL) and diethyl ether (25 mL). The aqueous phase was extracted with diethyl ether (3 × 25 mL) and the combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The resulting oil was purified by flash chromatography to give **49** (65 mg, 95% yield).

IR: ($CHCl_3$) ν 3 456, 3 046, 2 954, 1 458, 1 071, 936, 853.

^1H NMR ($CDCl_3$, 200 MHz, forskolin numbering) δ 1.01 (s, 3H, CH_3), 1.10 (d, J = 7.1 Hz, 3H, CH_3-8), 1.13 (s, 3H, CH_3), 1.39 (s, 3H, CH_3), 1.42 (s, 3H, CH_3), 1.50 (s, 3H, CH_3), 1.01–1.70 (m, 6H, H_2-2, H_2-3, H-4, OH), 1.80 (m, 1H, H-8), 2.70 (s, 1H, OH), 3.55 (dd, J = 9.3, 4.9 Hz, 1H, H-7), 4.12 (t, J = 2.8 Hz, 1H, H-1), 4.45 (dd, J = 4.9, 2.3 Hz, 1H, H-6), 5.30 (s, 1H, H-11).

^{13}C NMR: ($CDCl_3$, 50.3 MHz, forskolin numbering) δ 12.8 (CH_3-8), 13.6 (CH_3), 21.8 (C-3), 23.6 (CH_3), 26.3 (CH_3), 28.7 (CH_3), 32.7 (C-4), 33.5 (CH_3), 36.3 (C-2), 39.5 (C-8), 43.5 (C-10), 47.3 (C-5), 72.8 (C-7), 80.8 (C-6), 81.9 (C-1), 82.6 (C-9), 97.5 (C-11), 109.9 (C, $OC(CH_3)_2O$).

MS: (CI, NH_3) *m/z* 344 (MH^+ + NH_3), 327 (MH^+), 326.

(3aR,5aR*,6S*,6aS*,9aR*,9bR*,9cS*)-1,1,6,8,8,9c-Hexamethyl-5a-hydroxydecahydro-5H-furo[4',3',2':4,5]naphtho[1,2-d][1,3]dioxol-5-one 50*

- *Procedure A*

To a solution of compound **49** (50 mg, 0.15 mmol) in dichloromethane (1 mL) at 20 °C was added PCC (54 mg, 0.23 mmol, 1.5 equiv). The reaction mixture was stirred at this temperature for 2 h and partitioned between water (10 mL) and diethyl ether (40 mL). The aqueous phase was extracted with diethyl ether (3 × 25 mL) and the combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The resulting oil was purified by flash chromatography to give the formyl ketal **44** (43 mg, 95% yield).

- *Procedure B*

To a solution of the Dess–Martin reagent (325 mg, 1.2 mmol, 1.5 equiv) in CH_2Cl_2 (3 mL) was added a solution of diol **49** (50 mg, 0.15 mmol) in CH_2Cl_2 (5 mL). The resulting solution was stirred at 20 °C for 1 h, then partitioned between a saturated aqueous Na_2SO_3 solution (10 mL) and diethyl ether (40 mL). The aqueous phase was extracted with diethyl ether (3 × 25 mL) and the combined organic phases were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. Purification by flash chromatography on silica gel gave formyl ketal **44** (41 mg, 92% yield).

- *Procedure C*

To a solution of diol **49** (30 mg, 0.1 mmol) in acetone (1 mL) cooled to 0 °C was added a 2 M Jones reagent solution in H_2SO_4 (75 μL, 0.15 mmol, 1.5 equiv). The resulting solution was allowed to warm to 20 °C over 1 h and partitioned between water (5 mL) and diethyl ether (50 mL). The phases were separated, the aqueous phase was extracted with diethyl ether (3 × 50 mL) and the combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo. Purification by flash chromatography gave alcohol **50** (16 mg, 54% yield) and formyl ketal **44** (11 mg, 41% yield).

- *Procedure D*

A solution of Ag_2CO_3 (450 mg, 0.75 mmol, 10 equiv) over celite in toluene (5 mL) was concentrated under 0.1 mmHg pressure at 65 °C for 30 min. A solution of diol **49** (25 mg, 0.08 mmol) in toluene (1 mL) was then added to the above solution. The resulting mixture was refluxed for 3 h and filtered over a gel of celite. Purification by flash chromatography gave alcohol **50** (5 mg, 20% yield) and formyl ketal **44** (16 mg, 71% yield).

- *Procedure E*

To a solution of IBX (215 mg, 0.7 mmol, 12 equiv) in DMSO (1 mL) and pyridine (0.5 mL) at 20 °C was added a solution of diol **49** (20 mg, 0.06 mmol) in DMSO (1 mL). The resulting solution was stirred at this temperature for 1 h, then partitioned between a saturated aqueous Na_2SO_3 solution (15 mL) and diethyl ether (50 mL) and the phases were separated. The aqueous phase was extracted with diethyl ether (3 × 25 mL) and the combined organic phases

washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. Purification by flash chromatography on silica gel gave formylketal **44** (3 mg, 15% yield) and hydroxylactone **50** (17 mg, 85% yield).

• *Compound 50*

IR: ($CHCl_3$) ν 3 431, 2 995, 1 668, 1 421, 1 078, 936, 865, 745.

^1H NMR ($CDCl_3$, 200 MHz, forskolin numbering) δ 1.01 (s, 3H, CH_3), 1.18 (s, 3H, CH_3), 1.32 (d, J = 7.1 Hz, 3H, CH_3-8), 1.32 (2s, 6H, $2CH_3$), 1.49 (s, 3H, CH_3), 1.02–1.70 (m, 6H, H_2-2, H_2-3, H-4, OH), 1.95 (s, 1H, H-8), 3.69 (dd, J = 9.3, 5.1 Hz, 1H, H-7), 4.42 (dd, J = 5.1, 2.3 Hz, 1H, H-6), 4.50 (t, J = 2.6 Hz, 1H, H-1).

MS: (CI, NH_3) m/z 342 ($MH^+ + NH_3$), 325 (MH^+), 324.

Anal calc for $C_{18}H_{28}O_5$, 302.40: C, 66.64; H, 8.70. Found: C, 66.85; H, 8.62.

(3aR,6aS*,9aR*,9bR*,9cR*)-1,1,6,8,8,9c-Hexamethyl-1,2,3,3a,6a,9a,9b,9c-octahydro-5H-furo[4',3',2':4,5]naphtho[1,2-d][1,3]dioxol-5-one* **2**

To a solution of hydroxylactone **50** (12 mg, 0.04 mmol) in pyridine (0.5 mL) cooled at 0 °C was added $SOCl_2$ (140 μL, 1.6 mmol, 40 equiv) and the resulting solution was refluxed for 0.5 h and cooled at 20 °C. The mixture was then partitioned between water (10 mL) and diethyl ether (50 mL) and the phases were separated. The aqueous phase was extracted with diethyl ether (3 × 25 mL) and the combined organic phases were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. Purification by flash chromatography on silica gel gave lactone **2** (2–3 mg, 20–30% yield).

IR: ($CHCl_3$) ν 2 998, 1 752, 1 675, 1 200, 1 030.

^1H NMR ($CDCl_3$, 200 MHz, forskolin numbering) δ 1.07 (s, 3H, CH_3), 1.21 (s, 3H, CH_3), 1.35 (d, J = 2.6 Hz, 1H, H-5), 1.35 (s, 3H, CH_3), 1.40 (s, 3H, CH_3), 1.43 (s, 3H, CH_3), 1.52 (s, 3H, CH_3), 1.72–2.23 (m, 4H, H_2-2, H_2-3), 2.30 (s, 3H, CH_3), 4.10 (dd, J = 11.2, 5.7 Hz, 1H, H-1), 4.59 (d, J = 7.4 Hz, 1H, H-7), 4.63 (dd, J = 7.4, 2.6 Hz, 1H, H-6).

MS: (CI, NH_3) m/z 324 ($MH^+ + NH_3$), 307 (MH^+).

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