NIS-PPh_3: A Selective Reagent for the Spiroannulation of *o*-Allyl Phenols. Total Synthesis of Corallidictyal D

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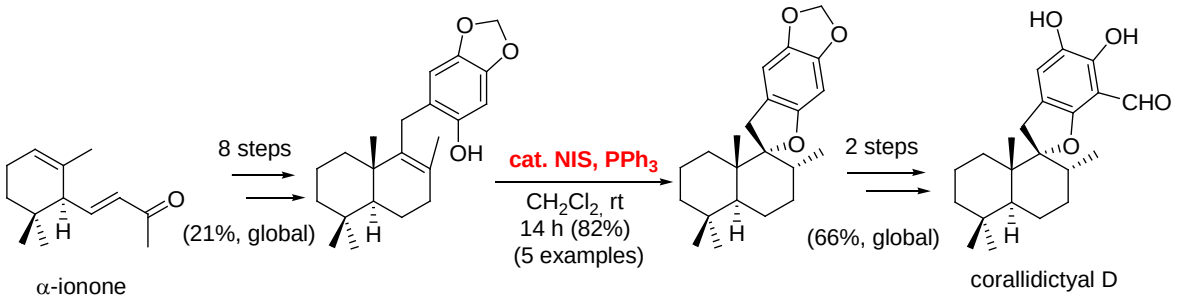


Treatment of *o*-allyl phenols with catalytic NIS-PPh_3 affords the corresponding spirodihydrobenzofuran derivatives in high yield, with high regio- and total

stereoselectivity, under mild conditions. These results were utilized to achieve the first total synthesis of the protein kinase C inhibitor corallidictyal D starting from α-ionone.

Introduction

During the last few decades, a variety of spirodihydrobenzofuran derivatives and related compounds, characterized by their wide-ranging, potent biological activities, have been isolated from different natural sources. Representative examples are corallidictyal B (**1**) and D (**2**), two spirosesquiterpene aldehydes isolated from the marine sponge *Aka coralliphaga*, with protein kinase C inhibitory activity,[1] the complement inhibitor K-76 (**4**),[2] the antiviral stachybotrydial (**5**)[3] and the myo-Inositol Monophosphatase (IMPase) inhibitor L-671,776 (**6**).[4] Various spirodihydrobenzofuranlactams have been isolated from the cultures of different *Stachybotrys* species, such as compounds **7-11**, with pancreatic cholesterol esterase inhibitor activity,[5] and lactams **12-15**, antagonists of endothelin and inhibitors of HIV-1 protease.[6] More recently, liphagal (**3**), a metabolite with selective PI3K kinase inhibitory activity, structurally related to compounds **1** and **2**, has also been reported.[7]

Despite the significant biological activities and the interesting sterically constrained spiro structure of the above mentioned compounds, only a few syntheses have been reported for some of these compounds. In all cases, the key step is the spiroannulation of the suitable drimane (bicyclic sesquiterpene) phenol. Corey et al. synthesized K-76 (**4**), after cyclization utilizing a THF – ethylene glycol – 2N hydrochloric acid mixture.[2b] Three years latter, McMurry et al. described the synthesis of compound **4**, utilizing cationic resin as the cyclizing agent.[2c] More recently, Kende et al. reported the synthesis of stachybotrylactam (**12**), also utilizing cationic resin.[8] In all cases, a mixture of spirodihydrobenzofuran and benzopyran in a 1.7-3.5:1.0 ratio was obtained.

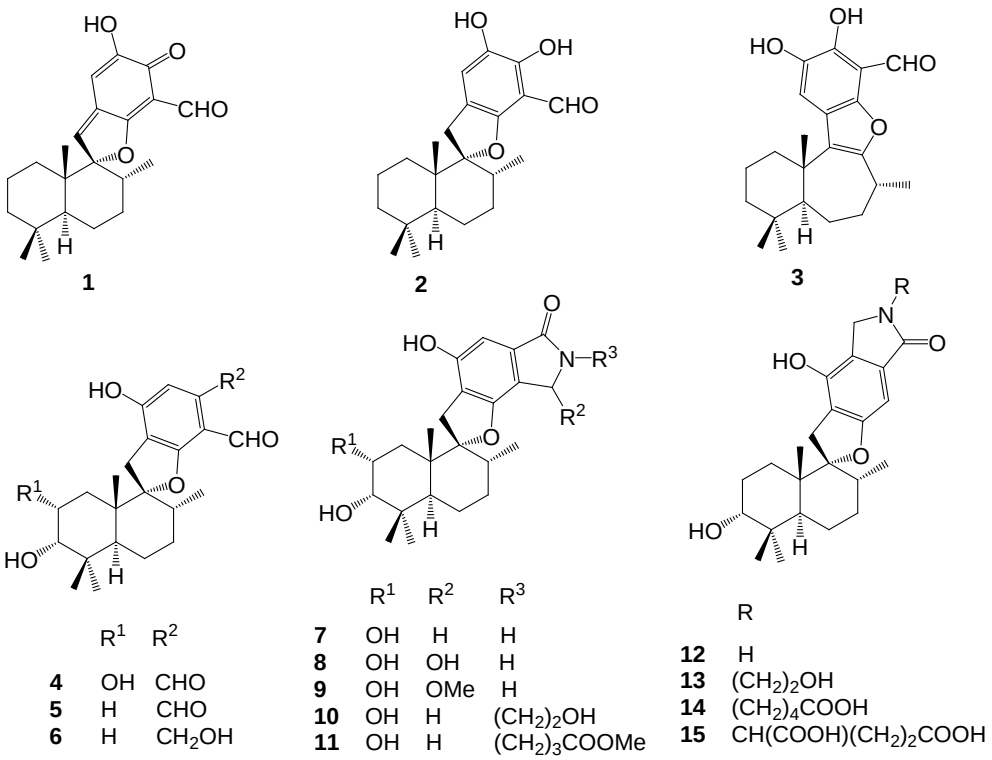


FIGURE 1. Bioactive spirodihydrobenzofurans and related metabolites.

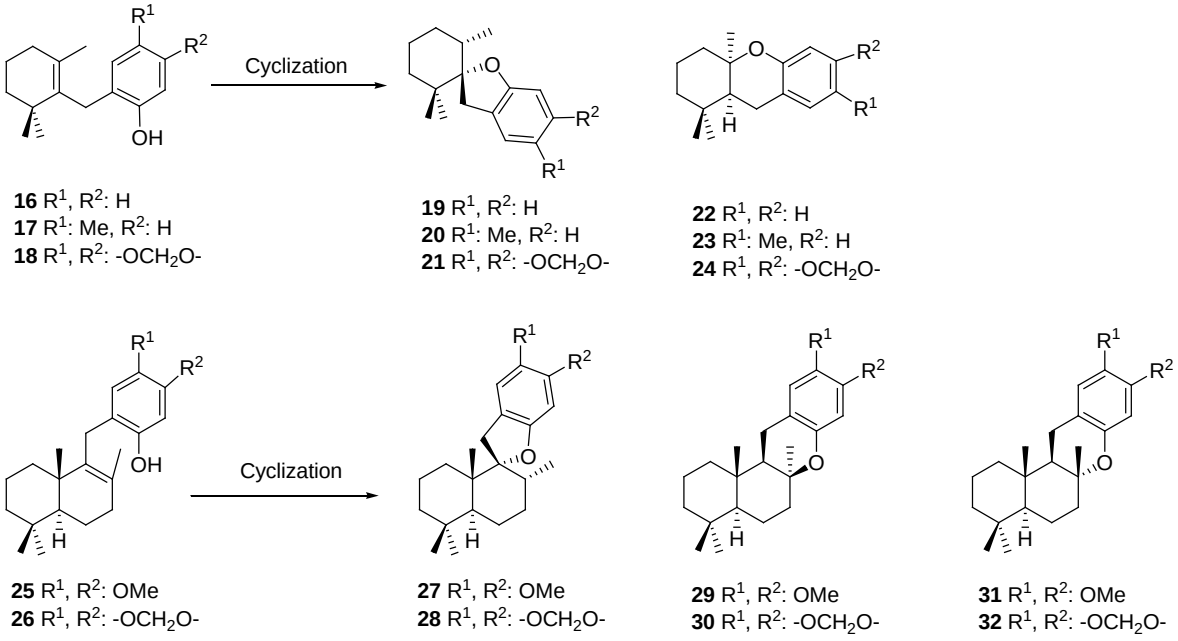
Results and Discussion

The interest of the metabolites mentioned above encouraged us to investigate alternative methods to achieve the spiroannulation process.

Intramolecular hydroalkoxylation of alkenylphenols similar to compounds **25-26**, catalyzed by Lewis[9,10] and by Bronsted acids,[10] has been reported previously. In all cases, the corresponding benzopyran derivatives, as a mixture of C8-epimers, were obtained with the C8β-Me isomer being the major constituent (see Table 1, entry 1[10]). As indicated above, Corey[2b] and McMurry[2c] reported having obtained the corresponding spirodihydrobenzofurans, when the cyclization was accomplished with hydrochloric acid

and cationic resin, respectively. However, when drimenyl phenol **26** was subjected in our laboratory to these reaction conditions benzopyran derivatives **30** and **32**[10] were obtained again (Table 1, entries 2-3). At this point it is important to emphasize that decalinic structures of this type are prone to undergo rearrangement under some acidic conditions.[11]

Table 1. Cyclization of some *o*-allyl phenols under acidic conditions or after reaction with NIS-PPh_3.



16 R^1, R^2: H
17 R^1: Me, R^2: H
18 R^1, R^2: -OCH_2O-

19 R^1, R^2: H
20 R^1: Me, R^2: H
21 R^1, R^2: -OCH_2O-

22 R^1, R^2: H
23 R^1: Me, R^2: H
24 R^1, R^2: -OCH_2O-

25 R^1, R^2: OMe
26 R^1, R^2: -OCH_2O-

27 R^1, R^2: OMe
28 R^1, R^2: -OCH_2O-

29 R^1, R^2: OMe
30 R^1, R^2: -OCH_2O-

31 R^1, R^2: OMe
32 R^1, R^2: -OCH_2O-

	o-Allyl phenol	Reaction conditions	Products
1	**26**	Acid[a]	**30** (minor) + **32** (major) (76-93%)
2	**26**	HCl conc, ethylene glycol/THF, 60 ºC, 1h[b]	**30**+**32** (1:5) (93%)
3	**26**	Amberlyst A-15, DCM, reflux, 60 h[c]	**32** (92%)
4	**16**	NIS, PPh_3, DCM, rt, 15 h[d]	**19**+**22** (4:1) (87%)
5	**17**	NIS, PPh_3, DCM, rt, 12 h[d]	**20**+**23** (4:1) (89%)

6	**18**	NIS, PPh_3, DCM, rt, 14 h[d]	**21**+**24** (3.5:1) (86%)
7	**25**	NIS, PPh_3, DCM, rt, 12 h[d]	**27**+**29** [13] (5:1) (85%)
8	**26**	NIS, PPh_3, DCM, rt, 10 h[d]	**28**+**30** (6:1) (90%)
9	**26**	NIS, PPh_3, DCM, rt, 14 h[e]	**28**+**30** (10:1) (90%)
10	**26**	I_2, DCM, rt, 15 min	**32** (89%)
11	**26**	NIS, PPh_3, DCM/H_2O, rt, 30 h[d]	No reaction
12	**26**	HI/H_2O, DCM, rt, 10 min	**28**+**30**+**32** (1:3:10) (83%)
13	**26**	Anhydrous HI, DCM, rt, 5 min [14]	**28**+**30**+**32** (1:3:5) (91%)

[a] $BF_3.OEt_2$, TsOH, H_2SO_4 conc and β-naphthalenesulfonic acid were utilized (see Ref. 10).

[b] Corey's method. No reaction occurred at room temperature (Ref. 2b).

[c] McMurry's method (Ref. 2c).

[d] NIS (0.1 equiv) and PPh_3 (0.1 equiv) were utilized.

[e] 1 g of compound **26** was cyclized.

Recently, while continuing our studies on the use of PPh_3 and iodine derivatives,[12] we found that some alkenyl phenols, after treatment with NIS and PPh_3, undergo cyclization providing the corresponding spirodihydrobenzofuran derivatives. Table 1 shows the reactions of several *o*-(β-cyclogeranyl)phenols (**16-18**) (entries 4-6) and *o*-drimenylphenols (**25-26**) (entries 7-9) with catalytic NIS- PPh_3 in dichloromethane at room temperature. As can be seen, in the worst case a 3.5 : 1 mixture of spirodihydrobenzofuran and benzopyran derivative is obtained. The relative stereochemistry of cyclized products was stablished on the basis of nOe experiments. The NOESY spectrum of spiro compounds **19-21** and **27-28** show correlations between each benzylic proton and its nearest methyl groups (Fig. 2).

Interestingly, the proportion of spirane derivative increases considerably when higher amount of unsaturated phenol is utilized; thus, phenol **26** (1 g approx.) (entry 9) was transformed into compound **28** almost entirely.

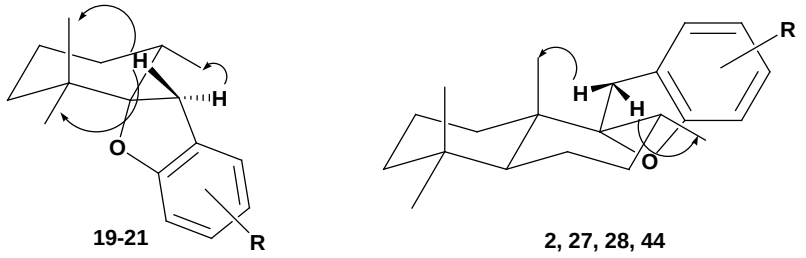


FIGURE 2. Observed nOes for spiro compounds.

In order to rule out the participation of hydriodic acid in the NIS-PPh_3 mediated process, other cyclization reactions were investigated. The most representative essays were those involving drimenyl phenols, shown in Table 1 (entries 10-12). Thus, the treatment of phenol **26** with I_2 in DCM gave benzopyran **32** almost exclusively (entry 10). No reaction was observed when *o*-allyl phenol **26** was treated with NIS- PPh_3 in DCM saturated with H_2O (entry 11). The same results were obtained after prolonged time reactions and when 1 equiv of NIS and PPh_3 were utilized. When the cyclization was performed in the presence of aqueous HI in DCM, the benzopyran derivative was again the main product (entry 12). A similar behavior was observed when the reaction was carried out utilizing anhydrous HI, prepared following the procedure reported by Koreeda et al.. [14] Treatment of compound **26** with this reagent in dichloromethane at room temperature for 5 min gave a 1:3:5 mixture of compounds **28, 30** and **32** (91%). The same result was obtained when the *O*-*t*-butyl dimethyl silyl derivative of phenol **26** was reacted under these conditions. However, when

this compound was treated with NIS/PPh_3, the starting material was recovered after 24 h of reaction time.

These results are consistent with those from acidic cyclizations previously reported. These cyclizations take place through an intermediate carbocation and can be summarized as follows: the most favorable carbocation on C-8 leads to the mixture of benzopyran epimers, whereas the carbocation on C-9 can provide the spirane derivative together with other side reaction products (rearrangement, etc..).

The behavior of acyclic *o*-allyl phenols was also investigated. *o*-Allylphenol and 2-allyl-6-methylphenol remained unaltered after treatment with NIS-PPh_3 at room temperature for 12 h.. After longer reaction times, partial isomerization of the carbon-carbon double bond is observed, but no cyclization reaction took place.

The use of other phosphines has also been investigated. When tributylphosphine was utilized, instead of triphenylphosphine, cyclization proceeded in a similar way, but resulted in a lower proportion of spiro compound. Therefore, compound **26** was transformed into a 4:1 mixture of compounds **28** and **30** (89%)**,** after treatment with PBu_3-NIS at room temperature for 16 h. This result shows up the influence of bulky phenyl substituents of PPh_3 in the regiochemistry of the cyclization process.

A first fact to be considered in accounting for the results obtained with the NIS- PPh_3 system is the complete *anti* stereoselectivity of the addition process, which is unprecedented in this type of reactions. Under the conditions previously described in the literature, the hydroalkoxylation process is not stereoselective, and the products obtained result from *syn* and *anti* addition.

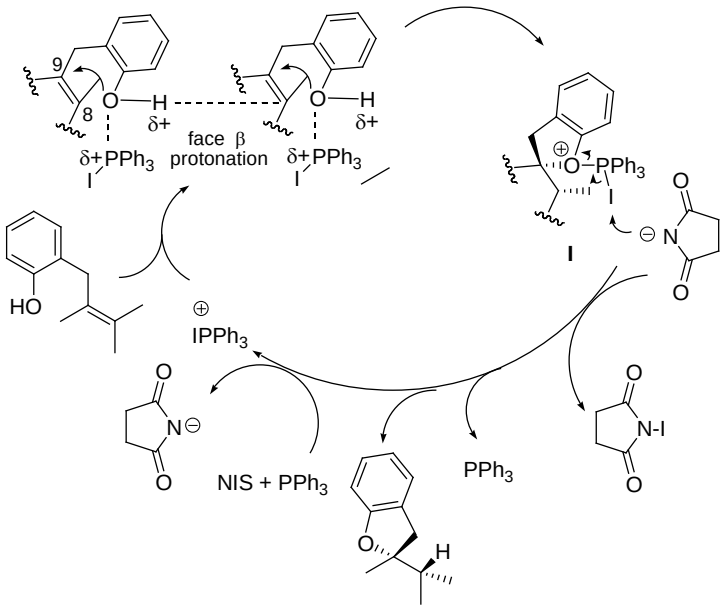
When the NIS-PPh_3 system is utilized, an *anti* concerted process, precluding the formation of an intermediate carbocation, must take place. A possible mechanism,

consistent with the experimental results, is postulated. The phenolic hydroxyl group acts as a nucleophile and a proton donor simultaneously. The OH group, activated by the phosphonium ion $^{+}PPh_3I$, transfers the proton by the β face of the olefinic bond of the adjacent molecule. The latter undergoes the simultaneous intramolecular nucleophilic *O*-attack on the carbon 9, affording intermediate **I**, precursor of the spirane compound (Scheme 1(a)). Alternatively, when the proton is transferred by the α face of the olefinic bond, the *O*-nucleophilic attack takes place on the carbon 8, providing intermediate **II**, precursor of the benzopyran derivative (Scheme 1 (b)). The preference for the β-face attack could be attributed to the steric hindrance that the phenolic moiety exerts on the α-face in the most favored conformation.

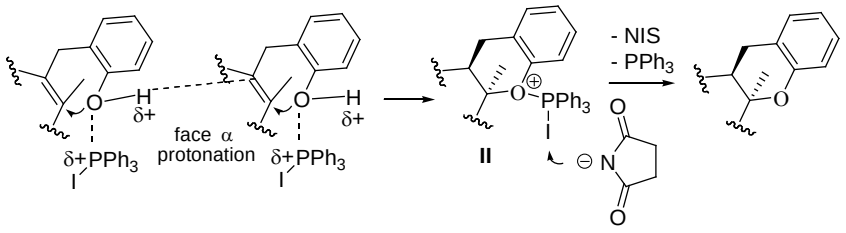
A similar behavior was previously found in the base-mediated cyclization of the 8,9-epoxyderivatives of alkenyl phenols similar to compound **25**: the 8β,9β-epoxyderivative undergoes nucleophilic attack on the C-9 providing the corresponding spiro compound, whereas the 8α,9α-epoxyderivative undergoes the C-8 attack, affording the benzopyran derivative.[10]

SCHEME 1. A possible mechanism for the NIS-PPh_3 mediated cyclization of *o*-allyl phenols.

(a) Formation of spirodihydrobenzofuran derivative:



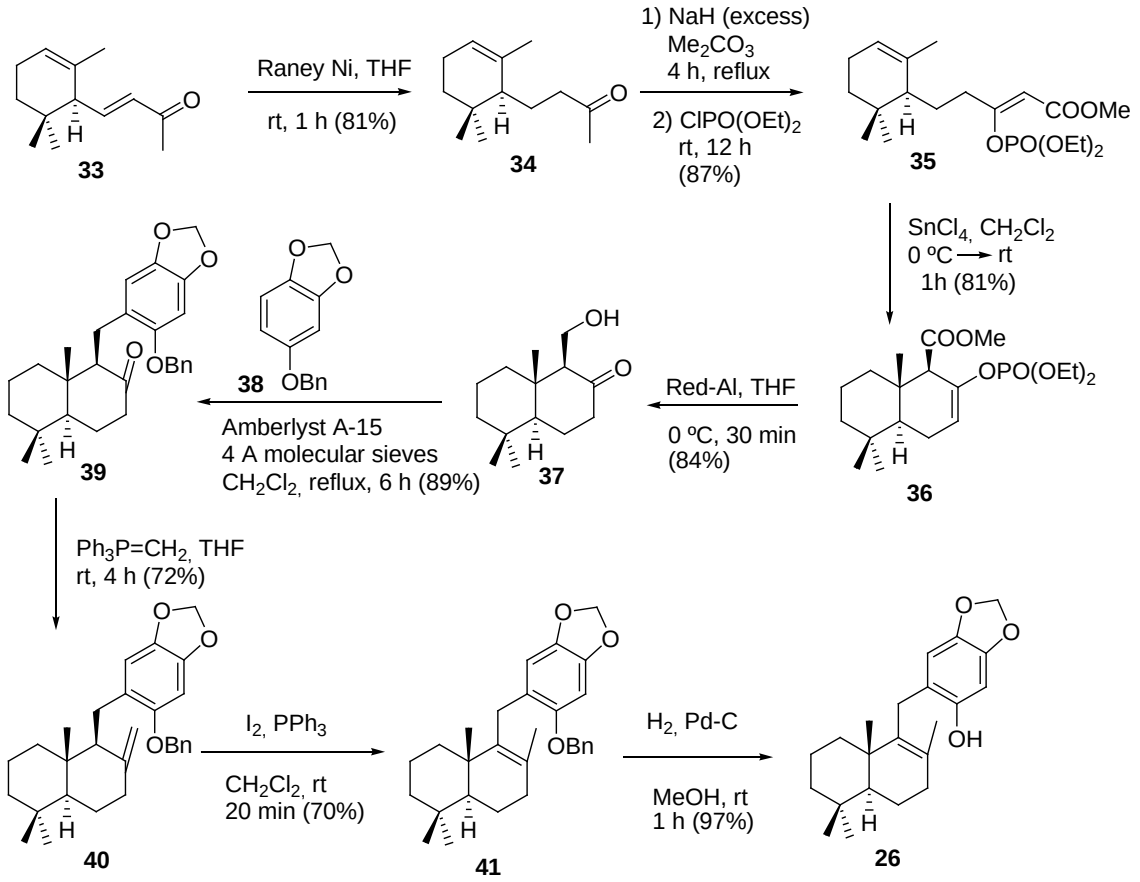
(b) Formation of benzopyran derivative:



Spirodihydrobenzofuran compound **28**, obtained from the *o*-allyl phenol **26**, is a suitable precursor of corallidictyal D (**2**). An efficient synthesis of drimenyl phenol **26** starting from commercial α-ionone (**33**), which is also accessible in enantiomerically pure form,[15] has been developed (Scheme 2). The selective 1,4-reduction of dienone **33** has been achieved by treatment with Raney Ni.[16] The enol phosphate **35** was obtained in a one-pot reaction after treating the methyl ketone **34**[17] with an excess of NaH and with dimethyl carbonate and $ClPO(OEt)_2$ successively. Compound **35** was transformed with complete regio- and stereoselectivity into bicyclic enol phosphate **36**,[18] after treatment with $SnCl_4$ in dichloromethane at 0 ºC. This transformation achieved the *trans* compound successfully.

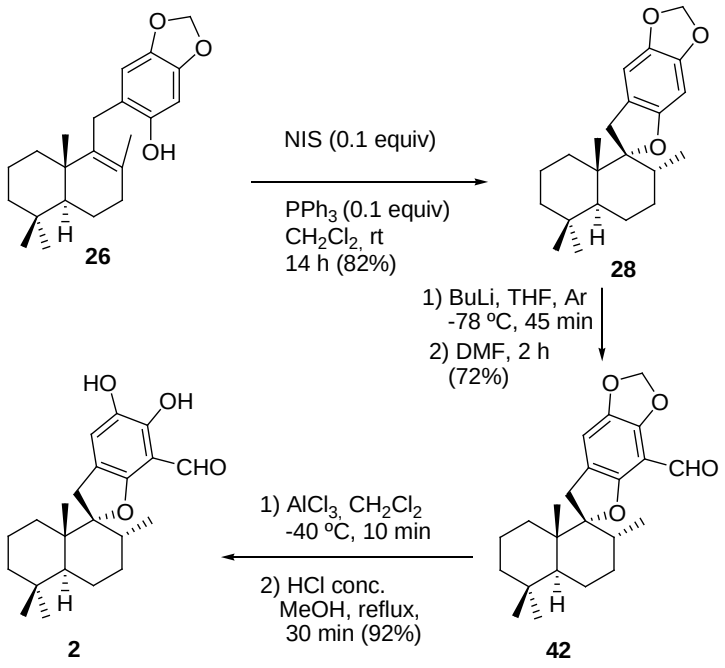
Note that all previously reported processes utilized to attain the *trans*-decalone skeleton from α-ionone (**33**) were not stereoselective. Instead, they afforded a mixture of the desired A/B *trans*-fused β-ketoester and its *cis*-fused stereoisomer, among other compounds.[19] Treatment of compound **36** with red-Al at 0 ºC gave hydroxyketone **37**.[20] This ketone was directly arylated by reacting with benzyl ether **38**,[21] easily prepared from commercial sesamol, in the presence of cationic resin Amberlyst A-15, affording ketone **39**. Methenylation of the latter, isomerization of the new carbon-carbon double bond and hydrogenation finally resulted in the desired phenol **26**.

SCHEME 2. Synthesis of *o*-allyl phenol **26** from α-ionone **(33)**.



Eventually, the synthesis of corallidictyal D (**2**) from phenol **26**, via the spirodihydrobenzofuran compound **28**, was tackled (Scheme 3). Treatment of this with BuLi in THF at -78 ºC followed by the addition of DMF and further reaction for 2 h gave aldehyde **42** (72% after column chromatography). Imakura´s method,[22] which we successfully utilized for the cleavage of methylenedioxy group, in our synthesis of liphagal (**3**),[7c] failed with aldehyde **42**. Instead, this cleavage was achieved using Goodman´s method.[23] Treatment of aldehyde **42** with $AlCl_3$ in dichloromethane at -40 ºC for 10 min and subsequent refluxing of a methanolic solution of the crude product in the presence of catalytic concentrated HCl led to corallidictyal D (**2**). Alternatively, an enantiospecific synthesis of compound **2** was accomplished utilizing the enantiomerically pure drimenyl phenol **26**, synthesized starting from the commercial diterpene (-)-sclareol.[10] The optical rotation of synthetic corallidictyal D (**2**)($[\alpha]_D^{25}$ = - 21.8 (c 14.8, $CHCl_3$)) does not allow to confirm the absolute stereochemistry of natural compound **2**, given that this was isolated from its natural source as a mixture of C-9 epimers.[1]

SCHEME 3. Synthesis of corallidictyal D (**2**).



In summary, a very efficient procedure to achieve the spiroannulation of *o*-allyl phenols is reported. Treatment of these with catalytic NIS and PPh_3 affords the corresponding spirodihydrobenzofuran derivatives in high yield, with high regioselectivity and complete stereoselectivity. This spiroannulation process seems to be the most suitable procedure reported to date for achieving a wide variety of spirodihydrobenzofuran derivatives, such as compounds **1**-**2** and **4**-**15**, which exhibit important biological activities. Utilizing this new cyclization procedure, the first total synthesis of the protein kinase C inhibitor corallidictyal D (**2**) is reported. Remarkable key steps of the synthetic sequence are: the Lewis acid-catalyzed cyclization of the β-ketoester enol phosphate **35**, the chemoselective reduction of enol phosphate **36** to give hydroxyketone **37** and the direct arylation of the latter leading to ketone **39**.

Experimental Section

General procedure for the preparation of monoterpenic phenols 16-18.

A 1.7 M solution of *tert*-butyllithium (1.2 mmol) was added at -78ºC to a solution of aryl bromides (1.2 mmol) in Et_2O under an argon atmosphere. After stirring for 25 min, β-cyclocitral (1 mmol) was added and the reaction mixture was further stirred for 40 min at -78ºC, at which time TLC showed no starting material remaining. Then, water (10 mL) was added to quench the reaction and the mixture was extracted with ether, the combined organic phases were dried, filtered and concentrated to give a crude product which was used in the next step without purification.

To a solution of the above crude product in CH_2Cl_2 (10 mL) were added successively $NaBH_3CN$ (5 mmol) and ZnI_2 (2 mmol) at 0 ºC and the mixture allowed to warm to room temperature and stirred for 5h, at which time TLC showed no starting material. Then, the mixture was filtered through a silica gel column and washed with ether (15 mL). The combined filtrate was evaporated to give a crude product which was used in the next step without purification. This was solved in THF (10 mL) and tetrabutylammonium fluoride (1.5 mmol) was added. After stirring for 15 min at room temperature, water was added and the mixture was extracted with ether. The combined organic phases were dried and the solvent was removed under vacuum to give a crude product which was chromatographed on silica gel column (20 % ether/hexanes) to give phenol **16-18.**

General cyclization procedure with the NIS/PPh_3 system.

N-iodosuccinimide (0.1 mmol) was added to a solution of triphenylphosphine (0.1 mmol) in

dry CH_2Cl_2 (4 mL) and the mixture was stirred at room temperature for, at least, 15 min. A solution of phenol (1 mmol) in CH_2Cl_2 (4 mL) was then added at 0 ºC and the reaction mixture was stirred at room temperature for the specified time, until TLC shows no remaining phenol. The solvent was removed under vacuum and the crude product was directly purified by flash chromatography column on silica gel (ether/hexanes mixture) to give the desired spirobenzofuran derivative**.**

2-((2,6,6-Trimethylcyclohex-1-enyl)methyl)phenol (16).

Utilizing β-cyclocitral (0.5 g, 3.22 mmol) and following the general procedure described for the preparation of monoterpenic phenols, **16** was obtained (481mg, 65 % global yield) as a brown syrup. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.04 (dd, *J* = 8.0, 7.4 Hz, 1H), 7.03 (d, *J* = 7.4 Hz, 1H), 6.82 (dd, *J* = 7.4, 7.4 Hz, 1H), 6.76 (d, *J* = 8.0 Hz, 1H), 5.49 (s, 1H), 3.41 (s, 2H), 2.07 (t, *J* = 6.3 Hz, 2H), 1.75-1.61 (m, 2H), 1.56 (s, 3H), 1.53-1.46 (m, 2H), 0.94 (s, 6H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 154.3 (C), 134.1 (C), 130.9 (C), 129.1 (CH), 126.8 (C), 126.6 (CH), 120.1 (CH), 115.2 (CH), 39.8 (CH_2), 35.1 (C), 32.8 (CH_2), 28.5 (CH_2), 28.4 (2 x CH_3), 27.0 (CH), 20.5 (CH_3), 19.4 (CH_2). IR (film): 3470, 3434, 1589, 1499, 1454, 1336, 1273, 1206, 1087, 1040, 843, 756 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{16}H_{22}ONa$ ($M+Na^+$) 253.1568, found: 253.1570.

4-Methyl-2-((2,6,6-trimethylcyclohex-1-enyl)methyl)phenol (17).

Utilizing β-cyclocitral (0.72 g, 4.73 mmol) and following the general procedure described for the preparation of monoterpenic phenols, **17** was obtained (623 mg, 54 % global yield) as a brown syrup. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 6.86 (d, *J* = 8.0 Hz, 1H), 6.83 (s, 1H), 6.65 (d, *J* = 8.0 Hz, 1H), 5.17 (s, 1H), 3.40 (s, 2H), 2.25 (s, 3H), 2.08 (t, *J* = 6.3 Hz, 2H), 1.76-1.64 (m, 2H), 1.60 (s, 3H), 1.54-1.45 (m, 2H), 0.96 (s, 6H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 151.9 (C), 134.4 (C), 131.2 (C), 129.8 (CH), 129.4 (C), 127.0 (CH), 126.2 (C), 115.0 (CH), 39.9 (CH_2), 35.1 (C), 32.8 (CH_2), 29.0 (CH_2), 28.4 (2 CH_3), 20.7 (CH_3), 20.5 (CH_3), 19.3 (CH_2). IR (film): 3410, 1705, 1611, 1505, 1469, 1361, 1259, 1204, 1092, 1041, 929, 807, 759 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{17}H_{24}ONa$ ($M+Na^+$) 267.1725, found: 267.1712.

6-((2,6,6-Trimethylcyclohex-1-enyl)methyl)benzo[d][1,3]dioxol-5-ol (18).

Utilizing β-cyclocitral (0.39 g, 2.56 mmol) and following the general procedure described for the preparation of monoterpenic phenols, **18** was obtained (428 mg, 61 % global yield) as brown syrup. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 6.55 (s, 1H), 6.38 (s, 1H), 5.86 (s, 2H), 5.11 (s, 1H), 3.30 (s, 2H), 2.05 (t, *J* = 6.3 Hz, 2H), 1.75-1.58 (m, 2H), 1.56 (s, 3H), 1.52-1.46 (m, 2H), 0.94 (s, 6H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 148.2 (C), 145.5 (C), 141.2 (C), 134.1 (C), 131.2 (C), 118.6 (C), 108.5 (CH), 100.7 (CH_2), 98.0 (CH), 39.8 (CH_2), 35.0 (C), 32.8 (CH_2), 28.4 (CH_3), 28.4 (CH_3), 28.3 (CH_2), 20.4 (CH_3), 19.3 (CH_2). IR (film): 3446, 1631, 1504, 1477, 1439, 1361, 1295, 1222, 1164, 1040, 937, 860, 761 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{17}H_{22}O_3Na$ ($M+Na^+$) 297.1467, found: 297.1471

Cyclization of phenols with the NIS/PPh_3 system.

Following the general cyclization procedure with the NIS/PPh_3 system, monoterpenic phenols **16-18** and sesquiterpenic phenols **25-26** were cyclized.

Cyclization of **16** (115 mg, 0.5 mmol) yielded a mixture of isomers **19** and **22** (100 mg) in a 4:1 ratio and 87% yield after 15 h.

Monoterpenic phenol **17** (122 mg, 0.5 mmol) was cyclized in the same manner furnishing the corresponding isomeric mixture of **20** and **23** (109 mg) in a 4:1 ratio and 89% yield in 12 h.

Treatment of **18** (135 mg, 0.5 mmol) following the same procedure provided the corresponding isomeric mixture of **21** and **24** (118 mg) in a 3.5:1 ratio and 86% yield after 14 h.

Sesquiterpenic phenol **25** (150 mg, 0.28 mmol) was also cyclized in the same manner giving access to the corresponding isomeric mixture of **27** and **29, 31** (121 mg) in a 5:1 ratio and 85% yield in 12 h.

Cyclization of **26** (110 mg, 0.32 mmol) yielded a mixture of isomers **28** and **30, 32** (136 mg) in a 6:1 ratio and 90% yield after 10 h, achieving up to 10:1 and 90% yield in 14 h when the reaction was performed in a gram-scale.

After a careful separation in silica gel (100% hexanes) both isomers were isolated and characterized in each case.

4,4,6-Trimethyl-spiro[benzofuran-5(8H),5(6H)-cyclohexane] (19).

Colourless syrup. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.08 (brd, *J* = 7.4 Hz, 1H), 7.06 (t, *J* = 8.3 Hz, 1H), 6.76 (t, *J* = 7.4 Hz, 1H), 6.72 (d, *J* = 7.9 Hz, 1H), 3.22 (d, *J* = 16.3 Hz, 1H), 2.88 (d, *J* = 16.3 Hz, 1H), 1.87-1.72 (m, 2H), 1.64-1.42 (m, 4H), 1.26 (brd, *J* = 12.6 Hz, 1H), 1.00 (s, 3H), 0.84 (s, 3H), 0.75 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 161.0 (C), 127.7 (CH), 127.4 (C), 124.1 (CH), 119.2 (CH), 108.2 (CH), 94.0 (C), 38.1 (C), 37.1 (CH), 36.3 (CH_2), 34.9 (CH_2), 30.7 (CH_2), 24.8 (CH_3), 22.4 (CH_3), 21.4 (CH_2), 15.6 (CH_3). NOESY ($CDCl_3$, 500 MHz): Observed correlations: 3.22 (d, *J* = 16.3 Hz, 1H) with 1.00 (s, 3H) and 0.84 (s, 3H); 2.88 (d, *J* = 16.3 Hz, 1H) with 0.75 (d, *J* = 6.6 Hz, 3H). IR (film): 1729, 1600, 1484, 1462, 1387, 1325, 1267, 1244, 1134, 1017, 945, 919, 871, 747, 707 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{16}H_{22}ONa$ ($M+Na^+$) 253.1568, found: 253.1572.

3',4,4,6,-Tetramethyl-spiro[benzofuran-5(8H),5(6H)-cyclohexane] (20).

Colourless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 6.89 (s, 1H), 6.86 (d, *J* = 8.0 Hz, 1H), 6.61 (d, *J* = 8.0 Hz, 1H), 3.18 (d, *J* = 16.3 Hz, 1H), 2.84 (d, *J* = 16.3 Hz, 1H), 2.26 (s, 3H), 1.85-1.71 (m, 2H), 1.65-1.49 (m, 2H), 1.44 (m, 1H), 1.35-1.19 (m, 2H), 0.99 (s, 3H), 0.84 (s, 3H), 0.75 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 161.7 (C), 130.9 (C), 130.7 (CH), 130.0 (C), 127.4 (CH), 110.3 (CH), 96.6 (C), 40.8 (C), 39.8 (CH), 39.0 (CH_2), 37.6 (CH_2), 33.4 (CH_2), 27.4 (CH_3), 25.1 (CH_3), 24.1 (CH_2), 23.4 (CH_3), 18.3 (CH_3)**.** NOESY ($CDCl_3$, 500 MHz): Observed correlations: 3.18 (d, *J* = 16.3 Hz, 1H) with 0.99 (s, 3H) and 0.84 (s, 3H); 2.84 (d, *J* = 16.3 Hz, 1H) with 0.75 (d, *J* = 6.6 Hz, 3H). IR (film): 1730, 1615,

1494, 1469, 1386, 1263, 1243, 1224, 1133, 945, 920, 807 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{17}H_{24}ONa$ ($M+Na^+$) 267.1725, found: 267.1723.

3',4'-Methylenedioxy-4,4,6-trimethyl-spiro[benzofuran-5(8H),5(6H)-cyclohexane] (21).

Colourless syrup. ^1H NMR ($CDCl_3$, 500 MHz) δ: 6.55 (s, 1H), 6.31 (s,1H), 5.85 (s, 1H), 5.84 (s, 1H), 3.12 (d, *J* = 15.9 Hz, 1H), 2.77 (d, *J* = 15.9 Hz, 1H), 1.86-1.66 (m, 2H), 1.65-1.37 (m, 4H), 1.22 (m, 1H), 0.96 (s, 3H), 0.84 (s, 3H), 0.76 (d, J = 6.6 Hz, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 155.7 (C), 147.1 (C), 140.6 (C), 118 (C), 104.4 (CH), 100.9 (CH_2), 95.1 (C), 91.9 (CH), 38.2 (C), 37.3 (CH), 36.3 (CH_2), 35.2 (CH_2), 30.7 (CH_2), 24.8 (CH_3), 22.4 (CH_3), 21.5 (CH_2), 15.7 (CH_3). NOESY ($CDCl_3$, 500 MHz): Observed correlations: 3.12 (d, *J* = 15.9 Hz, 1H) with 0.96 (s, 3H) and 0.84 (s, 3H); 2.77 (d, *J* = 15.9 Hz, 1H) with 0.76 (d, *J* = 6.6 Hz, 3H). R (film): 1875, 1730, 1619, 1501, 1479, 1387, 1305, 1268, 1184, 1150, 1040, 942, 920, 844, 766, 743 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{17}H_{22}O_3Na$ ($M+Na^+$) 297.1467, found: 297.1475.

1,1,4a-Trimethyl-2,3,4,4a,9,9a-hexahydro-1H-xanthene (22).

Colourless syrup. ^1H NMR ($CDCl_3$, 500 MHz) δ: 7.05 (dd, *J* = 7.6, 7.6 Hz, 1H), 7.04 (d, *J* = 7.6 Hz, 1H), 6.81 (dd, *J* = 7.3, 7.3 Hz, 1H), 6.75 (d, *J* = 8 Hz, 1H), 3.04 (dd, *J* = 17.6 Hz, 8.0 Hz, 1H), 2.77 (d, *J* = 17.6 Hz, 1H), 2.04 (brd, *J* = 14.6 Hz, 1H), 1.86 (m, 1H), 1.59-1.36 (m, 4H), 1.27 (t, *J* = 11.9 Hz o dd, *J* = 26.0, 15.5 Hz, 1H), 1.21 (s, 3H), 0.97 (s, 3H), 0.65

(s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 154.5 (C), 128.9 (CH), 126.6 (CH), 122.0 (C), 119.8 (CH), 117.1 (CH), 75.2 (C), 44.5 (CH), 41.7 (CH_2), 39.6 (CH_2), 34.0 (C), 32.3 (CH_3), 27.0 (CH_3), 23.6 (CH_2), 21.4 (CH_3), 18.1 (CH_2). IR (film): 1610, 1586, 1489, 1455, 1373, 1312, 1239, 1160, 1107, 1057, 1021, 946, 848, 753, 707 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{16}H_{22}ONa$ ($M+Na^+$) 253.1568, found: 253.1572.

1,1,4a,6-Tetramethyl-2,3,4,4a,9,9a-hexahydro-1H-xanthene (23).

Colourless syrup. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 6.85 (s, 2H), 6.63 (d, *J* = 8.8 Hz, 1H), 2.99 (dd, *J* = 17.6, 8.0 Hz, 1H), 2.72 (d, *J* = 17.6 Hz, 1H), 2.25 (s, 3H), 2.03 (m, 1H), 1.85 (m, 1H), 1.56-1.36 (m, 5H), 1.19 (s, 3H), 0.95 (s, 3H), 0.66 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 154.9 (C), 131.9 (C), 131.5 (CH), 130.0 (CH), 124.3 (C), 119.4 (CH), 77.7 (C), 47.2 (CH), 44.4 (CH_2), 42.3 (CH_2), 36.6 (C), 34.9 (CH_3), 29.6 (CH_3), 26.2 (CH_2), 24.1 (CH_3), 23.2 (CH_3), 20.8 (CH_2). IR (film): 1730, 1503, 1457, 1372, 1306, 1267, 1237, 1160, 1122, 947, 812 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{17}H_{24}ONa$ ($M+Na^+$) 267.1725, found: 267.1723.

5a,9,9-Trimethyl-6,7,8,9,9a,10-hexahydro-5aH-[1,3]dioxolo[4,5-b]xanthene (24).

Colourless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 6.49 (s, 1H), 6.30 (s, 1H), 5.84 (d, *J* = 8.0 Hz, 2H), 2.92 (dd, *J* = 17.4, 8.0 Hz, 1H), 2.63 (d, *J* = 17.4 Hz, 1H), 1.97 (ddd, *J* = 15.4, 6.3, 3.5 Hz, 1H), 1.82 (m, 1H), 1.47-1.38 (m, 2H), 1.35 (d, *J* = 8.0 Hz, 1H), 1.25 (dd, *J* = 9.7, 3.5 Hz, 2H), 1.17 (s, 3H), 0.94 (s, 3H), 0.64 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 148.9

(C), 146.2 (C), 141.1 (C), 113.3 (C), 107.7 (CH), 100.6 (CH_2), 99.0 (CH), 75.2 (C), 44.4 (CH), 41.8 (CH_2), 39.6 (CH_2), 34.0 (C), 32.4 (CH_3), 26.8 (CH_3), 23.9 (CH_2), 21.4 (CH_3), 18.2 (CH_2). IR (film): 1876, 1731, 1631, 1503, 1479, 1438, 1387, 1366, 1235, 1180, 1148, 1040, 941, 915, 868, 845, 775 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{17}H_{22}O_3Na$ ($M+Na^+$) 297.1467, found: 297.1472.

4,5-Dimethoxy-2-(((4a*S*,8a*S*)-2,5,5,8a-tetramethyl-3,4,4a,5,6,7,8,8a-octahydro naphthalen-1-yl)methyl)phenol (25).

652 mg of phenol **25** was obtained from (4a*S*,5*S*)-5-(2-(benzyloxy)-4,5-dimethoxybenzyl)-1,1,4a-trimethyl-6-methylene-decahydronaphthalene (1.2 g, 2.68 mmol) in 68% global yield, following the same procedure described for the preparation of sesquiterpenic phenol **26**. [10]

Colourless syrup. $[\alpha]_D^{25}$ = + 54.3 (c 14.9, $CHCl_3$). ^1H NMR ($CDCl_3$, 500 MHz) δ: 6.57 (s, 1H), 6.39 (s, 1H), 5.37 (br s, 1H, -OH), 3.82 (s, 3H), 3.79 (s, 3H), 3.35 (d, *J* = 16.5 Hz, 1H), 3.30 (d, *J* = 16.5 Hz, 1H), 2.20-2.09 (m, 2H), 1.74 (dd, *J* = 13.0, 6.9 Hz, 1H), 1.62 (s, 3H), 1.58-1.45 (m, 2H), 1.42-1.31 (m, 2H), 1.29-1.16 (m, 2H), 1.13-1.01 (m, 2H), 1.00 (s, 3H), 0.90 (s, 3H), 0.84 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 148.4 (C), 143.0 (C), 138.4 (C), 135.6 (C), 130.7 (C), 117.0 (C), 114.0 (CH), 101.1 (CH), 57.0 (CH_3), 56.1 (CH_3), 52.2 (CH), 41.9 (CH_2), 39.4 (C), 36.7 (CH_2), 33.8 (C), 33.6 (CH_2), 33.5 (CH_3), 28.4 (CH_2), 22.0 (CH_3), 20.6 (CH_3), 20.5 (CH_3), 19.2 (CH_2), 19.1 (CH_2). IR (film): 3462, 1604, 1521, 1451, 1412, 1366, 1201, 1095, 999, 862, 752 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{23}H_{34}O_3Na$ ($M+Na^+$) 381.2406, found: 381.2398.

[1'(2)*R*,2'*R*,4'a*R*,8'a*S*]-5,6-Methoxy-3',4',4'a,5',6',7',8',8'a-octahydro-2',5',5',8'a-tetramethyl-spiro[benzofuran-2(3H),1'(2'H)-naphtalene] (27).

Colourless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 6.66 (s, 1H), 6.42 (s, 1H), 3.83 (s,3H), 3.79 (s, 3H), 3.18 (d, *J* = 15.8 Hz, 1H), 2.74 (d, *J* = 15.8 Hz, 1H), 1.73 (m, 1H), 1.68-1.23 (m, 10H), 1.18 (ddd, *J* = 13.6, 3.6 Hz,1H), 0.95 (s, 3H), 0.91 (s, 3H), 0.84 (s, 3H), 0.73 (d, *J* = 6.5 Hz, 3H).^{13}C NMR ($CDCl_3$, 125 MHz) δ: 155.8 (C), 149.2 (C), 142.6 (C), 116.9 (C), 108.70 (CH), 96.6 (C), 93.9 (CH), 57.0 (CH_3), 56.1 (CH_3) 46.7 (CH), 42.6 (C), 41.8 (CH_2), 37.4 (CH), 35.0 (CH_2), 33.3 (C), 33.3 (CH_3), 31.3 (CH_2), 31.3 (CH_2), 22.1 (CH_3), 21.6 (CH_2), 18.4 (CH_2), 16.3 (CH_3), 15.8 (CH_3). NOESY ($CDCl_3$, 500 MHz): Observed correlations: 3.18 (d, *J* = 15.8 Hz, 1H) with 0.95 (s, 3H); 2.74 (d, *J* = 15.8 Hz, 1H) with 0.73 (d, *J* = 6.5 Hz, 3H). HRMS (FAB) *m/z*: calcd for $C_{23}H_{34}O_3Na$ ($M+Na^+$) 381.2406, found: 381.2392.

[1'(2)*R*,2'*R*,4'a*R*,8'a*S*]-5,6-Methylenedioxy-3',4',4'a,5',6',7',8',8'a-octahydro-2',5',5',8'a-tetramethyl-spiro[benzofuran-2(3H),1'(2'H)-naphtalene] (28).

Colourless syrup. $[\alpha]_D^{25}$ = + 2.07 (c 16.5, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 6.54 (s, 1H), 6.35 (s, 1H), 5.85 (s,1H), 5.84 (s, 1H), 3.15 (d, *J* = 16.0 Hz, 1H), 2.71 (d, *J* = 16.0 Hz, 1H), 1.71 (tt, *J* = 12.0, 6.5 Hz, 1H), 1.65-1.44 (m, 5H), 1.43-1.28 (m, 5H), 1.19 (m, 1H), 0.93 (s, 3H), 0.91 (s, 3H), 0.84 (s, 3H), 0.73 (d, *J* = 6.5 Hz, 3H).^{13}C NMR ($CDCl_3$, 125 MHz) δ: 155.7 (C), 147.0 (C), 140.6 (C), 117.8 (C), 104.3 (CH), 100.9 (CH_2), 96.6 (C),

91.9 (CH), 46.5 (CH), 42.5 (C), 41.8 (CH_2), 37.3 (CH), 34.8 (CH_2), 33.4 (C), 33.3 (CH_3), 31.3 (CH_2), 31.2 (CH_2), 22.1 (CH_3), 21.5 (CH_2), 18.4 (CH_2), 16.2 (CH_3), 15.7 (CH_3). NOESY ($CDCl_3$, 500 MHz): Observed correlations: 3.15 (d, *J* = 16.0 Hz, 1H) with 0.93 (s, 3H); 2.71 (d, *J* = 16.0 Hz, 1H) with 0.73 (d, *J* = 6.5 Hz, 3H). IR (film): 1618, 1501, 1472, 1458, 1386, 1304, 1263, 1211, 1151, 1041, 1006, 940, 843, 797, 751 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{22}H_{30}O_3Na$ ($M+Na^+$) 365.2093, found: 365.2102.

Treatment of 26 with I_2: Synthesis of 8-epi-19,20-di-*O*-methylenepuupehenol (32).

Iodine (41 mg, 0.16 mmol) was added to a solution of phenol (37 mg, 0.11 mmol) in dry CH_2Cl_2 (2 mL) and the mixture was stirred at room temperature for 15 min., until TLC shows no remaining starting material. After removal of most of the solvent under reduced pressure, the reaction mixture was filtered over silica gel and concentrated to give a crude product which was purified by flash chromatography column on silica gel (5% ether/hexanes) to afford **32** as a colourless syrup (33 mg, 89%).

Treatment of 26 with NIS/PPh_3 in CH_2Cl_2-H_2O or CH_2Cl_2-THF-H_2O.

N-iodosuccinimide (7 mg, 0.03 mmol) was added to a solution of triphenylphosphine (8 mg, 0.03 mmol) in CH_2Cl_2 (4 mL) and the mixture was stirred at room temperature for, at least, 15 min. Then water (0.2 mL) and a solution of **26** (83 mg, 0.24 mmol) in CH_2Cl_2 (4 mL) was added successively at 0 ºC and the reaction mixture was stirred at room

temperature for 30 h, at which time TLC showed unaltered **26** and formation of triphenylphosphine oxide.

Similar results were obtained when 1 equiv of NIS and 1 equiv of PPh_3 were utilized. When the reaction time was prolonged for 6 days, the unaltered starting material was recovered.

When the reaction was performed in CH_2Cl_2–THF-H_2O (4:2:1), utilizing different proportions of reagent a similar result was obtained even prolonging the reaction time for six days

Treatment of 26 with HI/H_2O.

To a solution of **26** (93 mg, 0.27 mmol) in dichloromethane (2 mL) was added at room temperature 55% aqueous solution of hydriodic acid (0.1 mL) and the reaction mixture was stirred for 10 minutes, at which time TLC showed no starting material remaining. Then water was added and the reaction was extracted with dichloromethane (2 x 10 mL). The combined organic layers were washed with water (3 x 5 mL), brine (2 x 5 mL) and dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum to give 0.77 mg (83%) of a crude product. Spectra of this showed an isomeric mixture of **28**, **30** and **32** (ratio 1:3:10). The ratio of isomeric mixture was determined by ^{1}H NMR spectra.

Treatment of 26 with anhydrous HI.

To a solution of 1,3-propanedithiol (0.75 mL, 0.622 mmol) in dry CH_2Cl_2 (5 mL) was added iodine (79 mg, 0.311 mmol) and the mixture was stirred at room temperature for 30

min, then a solution of phenol **26** (73 mg, 0.213 mmol) in dry CH_2Cl_2 (5 mL) was added and the resulting mixture was stirred at room temperature for 5 min, at which time TLC showed no starting material. Then the solvent was removed under vacuum and the residue was diluted with ether-water (30 mL, 3:1), and the phases were shaken and separated. The organic layer was washed with saturated aqueous $NaHCO_3$ (10 mL), water (10 mL) and brine. The dried organic layers were filtered and evaporated, to give 66 mg (91%) of a crude product. Spectra of this showed an isomeric mixture of **28**, **30** and **32** (ratio 1:3:5). The ratio of isomeric mixture was determined by ^{1}H NMR spectra.

Treatment of 26 with the NIS/PBu_3 system.

N-iodosuccinimide (7 mg, 0.031 mmol) was added to a solution of tributylphosphine (7 mg, 0.034 mmol) in dry CH_2Cl_2 (3 mL) and the mixture was stirred at room temperature for 15 min. A solution of phenol **26** (106 mg, 0.309 mmol) in CH_2Cl_2 (3 mL) was then added at 0 ºC and the reaction mixture was stirred at room temperature for 16 h, until TLC shows no remaining phenol. The solvent was removed under vacuum and the crude product was directly purified by flash chromatography column on silica gel (3% ether/hexanes) to give 94 mg (89%) of a mixture of **28** and **30 (**ratio 4 : 1). The ratio of isomeric mixture was determined by ^{1}H NMR spectra.

Dihydro-α-ionone (34).

To a solution of α-ionone (**33**) (2 g, 10.4 mmol) in THF (25 mL), Ni Raney solution was added (50% in water, 3 mL) and the reaction was stirred for 1h at room temperature, at which time TLC showed no starting material. Then, the reaction mixture filtered through a mixture of silica gel –Na_2SO_4 (100 g), washed with acetone (10 mL) and the solvent was removed under vacuum to give **34** (1.64 g, 81%) as a colorless oil.

(*Z*)-Methyl 3-(diethoxyphosphoryloxy)-5-(2,6,6-trimethylcyclohex-2-enyl)pent-2-enoate (35).

Sodium hydride (1.65 g, 41.2 mmol, 60 % dispersion in mineral oil) was carefully added, in portions, to a precooled solution (0 ºC) of dihydro-α-ionone (**34**) (2 g, 10.3 mmol) in dry THF (20 mL), under argon atmosphere. After the reaction mixture was stirred at this temperature for 10 min., dimethyl carbonate (103 mmol, 8.66 mL) was added and the reaction mixture was stirred at reflux for an additional 4 h, at which time, TLC showed the disappearance of the starting material. Diethyl chlorophosphonate (3.1 mL, 20.6 mmol), was then added dropwise and the mixture was stirred for another 12 h at room temperature. After this time, it was poured into ice (50 g) and extracted with ether (2 x 50 mL). The combined organic layers were washed with water (2 x 30 mL), brine (1 x 30 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to give a pale yellow oil crude product that was purified by chromatography column on silica gel (30% ether/hexanes) affording pure β-ketoester **35** (2.28 g, 87%) as a yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 5.35 (br s , 1H), 5.32 (t; *J* = 4.1 Hz, 1H), 4.25 (dq, *J* = 7.3, 1.8 Hz, 2H), 4.23 (dq, *J* = 7.3, 1.8 Hz, 2H), 3.68 (s, 3H), 2.46 (m, 1H), 1.98-1.88 (m, 2H),

1.75-1.68 (m, 2H), 1.67 (br s, 3H), 1.60 (m, 1H), 1.48 (m, 1H), 1.41 (m, 1H), 1.35 (t, *J* = 7.1 Hz, 6H), 1.14 (m, 1H), 0.92 (s, 3H), 0.86 (s, 3H), ^{13}C NMR (126 MHz, $CDCl_3$) δ: 164.34 (C), 164.32 (C), 162.6 (C), 121.1. (CH), 104.8 (CH), 64.8 (CH_2), 64.7 (CH_2), 51.1 (CH_3); 48.7 (CH), 35.6 (CH_2), 32.6 (C), 31.5 (CH_2), 28.0 (CH_2), 27.6 (CH_3), 27.5 (CH_3), 23.5 (CH_3), 23.0 (CH_2), 16.2 (CH_3), 16.1 (CH_3). IR (film): 3449, 1732, 1665, 1440, 1276, 1207, 1164, 1032, 986 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{19}H_{33}O_6PNa$ ($M+Na^+$) 411.1912, found: 411.1904.

Methyl 2-(diethoxyphosphoryloxy)-5,5,8a-trimethyl-1,4,4a,5,6,7,8,8a-octahydronaphthalene-1-carboxylate (36).

To a solution of β-ketoester **35** (2 g, 5.15 mmol) in dry CH_2Cl_2 (15 mL) was added tin tetrachloride (1.21 mL, 10.30 mmoles) at 0 °C. After being stirred at the same temperature for 10 min., the cooling bath was removed and the reaction mixture was allowed to warm to room temperature for 1h, at which time TLC showed no starting material. It was then cooled to 0 ºC and water was added to quench the reaction. The solvent was removed under vacuum and the crude product was fractionated in water-ether (30 : 100 mL), and the phases were shaken and separated. The organic layer was washed with saturated aqueous $NaHCO_3$ (2 x 25 mL), water (25 mL) and brine (25 mL). The dried organic layers were filtered and evaporated, and the residue was directly purified by flash chromatography column (30% ether/hexanes) to yield **36** (1.6 g, 81%) as a colorless syrup.

^{1}H NMR ($CDCl_3$, 500 MHz) δ: 5.66 (m, 1H). 4.17-4.04 (m, 4H) 3.66 (s, 3H), 3.21 (br s, 1H), 2.14 (m, 1H), 1.99 (m, 1H), 1.70 (m, 1H), 1.52 (m, 1H), 1.47-1.39 (m, 3H), 1.32 (t, *J*

= 7.5 Hz, 3H), 1.30 (t, *J* = 7.4 Hz, 3H), 1.24 (dd, *J* = 12.0, 4.2 Hz, 1H), 1.18 (m, 1H), 0.96 (s, 3H), 0.90 (s, 3H), 0.88 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 170.6 (C). 142.9 (C), 112.0 (CH), 64.4 (CH_2), 64.2 (CH_2), 60.5 (CH), 51.3 (CH_3), 48.9 (CH), 42.0 (CH_2), 40.4 (CH_2), 37.5 (C), 33.4 (CH_3), 33.1 (C), 22.2 (CH_3), 22.0 (CH_2), 18.6 (CH_2), 16.13 (CH_3), 16.07 (CH_3), 15.35 (CH_3). IR (film):3455, 1739, 1686, 1442, 1273, 1165, 1036, 970 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{19}H_{33}O_6PNa$ ($M+Na^+$) 411.1912, found: 411.1923.

1-(Hydroxymethyl)-5,5,8a-trimethyl-octahydronaphthalen-2(1H)-one (37).

Phosphoenol ester **36** (1.5 g, 3.86 mmol) in dry THF (200 mL) was added dropwise to a solution of sodium aluminium bis(2-methoxy)hydride in toluene (d:1.02 g/ml) (1 mL, 5.0 mmol) at 0 °C under argon atmosphere. After stirring at the same temperature for 30 min, the solution was quenched with 0.1 M HCl (10 mL) and was then concentrated under reduced pressure, diluted with ether - water (80 : 20 mL) and the phases were shaken and separated. The organic layer was washed with brine (15 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified through silica gel chromatography column (35% ether/hexanes) to afford 727 mg of **37** (84%) as a colorless oil.

1-((6-(Benzyloxy)benzo[d][1,3]dioxol-5-yl)methyl)-5,5,8a-trimethyl-octahydronaphthalen-2(1H)-one (39).

Amberlyst 15 ion-exchange resin (Aldrich) (0.5 g) and molecular sieves 4 Å (1 g) were added to a solution of β-hydroxyketone **37** (0.8 g, 3.57 mmol) and **38** (913 mg, 4 mmol) in

dry DCM (20 mL) and the mixture was stirred at reflux for 6 h, at which time TLC showed no **37**. Then, it was filtered and the solvent was removed under vacuum to give a crude product which was purified by flash chromatography column on silica gel (25% ether/hexanes) to give **39** (1.1 g, 89%) as a colorless syrup.

^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.42-7.32 (m, 5H), 6.89 (s, 1H), 6.52 (s, 1H), 5.86 (d, *J* = 1.5 Hz, 1H), 5.84 (d, *J* = 1.5 Hz, 1H), 4.95 (d, *J* = 11.2 Hz, 1H), 4.93 (d, *J* = 11.2 Hz, 1H), 2.72 (dd, *J* = 13.2, 9.6 Hz, 1H), 2.63 (dd, *J* = 13.2, 1.9 Hz, 1H), 2.42 (br d, *J* = 9.6 Hz, 1H), 2.31 (ddd, *J* = 12.9, 4.7, 2.0 Hz, 1H), 2.16 (m, 1H), 1.98 (m, 1H), 1.65 (br d, *J* = 13.5 Hz, 1H), 1.60 (ddd, *J* = 26.4, 13.2, 4.7 Hz, 1H), 1.42 (ddt, *J* = 27.4, 13.6, 3.3 Hz, 1H), 1.34 (dd, *J* = 12.7, 3.0 Hz, 1H), 1.33 (dd, *J* = 13.2, 1.3 Hz, 1H), 1.22 (m, 1H), 1.06-0.92 (m, 2H), 0.91 (s, 3H), 0.80 (s, 3H), 0.71 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 211.9 (C), 151.4 (C), 146.0 (C), 140.9 (C), 137.1 (C), 128.6 (2 CH), 128.5 (2 CH), 128.3 (CH), 123.1 (C), 112.3 (CH), 101.0 (CH_2), 95.5 (CH), 71.6 (CH_2), 64.5 (CH), 54.4 (CH), 43.3 (C), 42.9 (CH_2), 42.0 (CH_2), 38.8 (CH_2), 33.8 (C), 33.7 (CH_3), 24.4 (CH_2), 23.2 (CH_2), 21.8 (CH_3), 19.1 (CH_2), 14.7 (CH_3). IR (film): 1709, 1622, 1505, 1484, 1389, 1170, 1041, 939, 896, 751, 698 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{28}H_{34}O_4Na$ ($M+Na^+$) 457.2355, found: 457.2353.

5-(Benzyloxy)-6-((5,5,8a-trimethyl-2-methylene-decahydronaphthalen-1-yl)methyl)benzo[d][1,3]dioxole (40).

A 2 M solution of *n*-butyllithium in hexanes (0.7 mL, 1.4 mmol) was added dropwise under argon atmosphere to a stirred suspension of methyltriphenylphosphonium bromide (400

mg, 1.12 mmol) in dry THF (10 mL) at 0 ºC, and the reaction mixture was allowed to warm to room temperature after stirring for 15 min. Then, a solution of **39** (250 mg, 0.58 mmol) in dry THF (10 mL) was added dropwise at 0 ºC, and the reaction mixture was further stirred at room temperature for an additional 4 h. Then, water (1 mL) was added to quench the reaction and the solvent was removed under vacuum. The crude product was extracted with ether (2 x 30 mL). The dried organic layers were evaporated and the residue was directly purified by flash chromatography column on silica gel (10% ether/hexanes) to yield **40** (181 mg, 72%) as a colourless syrup and 30 mg (12%) of starting material.

^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.30 (m, 5H), 6.59 (s, 1H), 6.46 (s, 1H), 5.78 (s, 2H), 4.92 (s, 2H), 4.69 (s, 1H), 4.57 (s, 1H), 2.68 (br d, *J* = 15.4 Hz, 1H), 2.59 (dd, *J* = 15.1, 10.5 Hz, 1H), 2.27 (br d, *J* = 12.8 Hz, 1H), 2.09 (br d, *J* = 10.0 Hz, 1H), 1.90 (ddd, *J* = 13.0, 13.0, 5.0 Hz, 1H), 1.71-1.60 (m, 2H), 1.46 (dd, *J* = 27.7, 13.9 Hz, 1H), 1.34-1.18 (m, 3H), 1.08-0.98 (m, 2H), 0.95 (ddd, *J* = 18.7, 16.7, 3.8 Hz, 1H), 0.80 (s, 3H), 0.74 (s, 3H), 0.69 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 151.3 (C), 148.9 (C), 145.7 (C), 141.2 (C), 137.4 (C), 128.9 (CH), 128.7 (2 CH), 128.0 (CH), 127.8 (CH), 123.8 (C), 109.8 (CH), 107.7 (CH_2), 101.1 (CH_2), 96.3 (CH), 71.7 (CH_2), 56.3 (CH), 55.8 (CH), 42.3 (CH_2), 40.1 (C), 39.1 (CH_2), 38.5 (CH_2), 33.8 (CH_3), 33.7 (C), 24.6 (CH_2), 23.9 (CH_2), 21.9 (CH_3), 19.6 (CH_2), 14.7 (CH_3). IR (film): 1644, 1585, 1504, 1483, 1434, 1388, 1167, 1040, 1000, 938, 867, 743, 696 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{29}H_{36}O_3Na$ ($M+Na^+$) 455.2562, found: 455.2554.

5-(Benzyloxy)-6-((2,5,5,8a-tetramethyl-3,4,4a,5,6,7,8,8a octahydronaphthalen-1-yl)methyl)benzo[d][1,3]dioxole (41).

Iodine (66 mg, 0.25 mmol) was added to a solution of triphenylphosphine (78 mg, 0.31 mmol) in dry CH_2Cl_2 (6 mL) and the mixture was stirred at room temperature for 10 min. A solution of alkene **40** (110 mg, 0.25 mmol) in CH_2Cl_2 (5 mL) was then added at room temperature. The reaction mixture was stirred at room temperature for 20 min, at which time an aliquot was checked by ^{1}H NMR, showing no starting material. After removal of most of the solvent under reduced pressure, the crude product was purified by flash chromatography column on silica gel (10% ether/hexanes) to yield **41** (75 mg, 70%) as a colourless syrup.

^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.44 (br d, *J* = 7.4 Hz, 2H), 7.38 (br t, *J* = 7.4 Hz, 2H), 7.32 (br t, *J* = 7.3 Hz, 1H), 6.60 (s, 1H), 6.56 (s,1H), 5.89 (d, *J* = 1.5 Hz, 1H), 5.88 (d, *J* = 1.5 Hz, 1H), 5.05 (d, *J* = 12.0 Hz, 1H), 5.02 (d, *J* = 12.0 Hz, 1H), 3.38 (d, *J* = 17.4 Hz, 1H), 3.22 (d, *J* = 17.4 Hz, 1H), 2.17 (m, 1H), 2.06 (dd, *J* = 17.8, 6.3 Hz, 1H), 1.72 (m, 1H), 1.60-1.50 (m, 2H), 1.48 (s, 3H), 1.45-1.20 (m, 5H), 1.09 (m, 1H), 0.98 (s, 3H), 0.90 (s, 3H), 0.84 (s, 3H).). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 150.8 (C), 145.4 (C), 141.3 (C), 137.7 (C), 137.6 (C), 129.1 (C), 128.7 (2 CH), 128.0 (CH), 127.4 (2 CH), 123.3 (C), 109.0 (CH), 100.9 (CH_2), 96.4 (CH), 71.4 (CH_2), 52.1 (CH), 41.9 (CH_2), 39.1 (C), 36.2 (CH_2), 33.7 (CH_2), 33.5 (C), 33.4 (CH_3), 27.0 (CH_2), 21.9 (CH_3), 20.5 (CH_3), 20.3 (CH_3), 19.3 (CH_2), 19.1 (CH_2). IR (film): 1729, 1626, 1505, 1481, 1387, 1382, 1316, 1174, 1041, 939, 870, 739, 696 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{29}H_{36}O_3Na$ ($M+Na^+$) 455.2562, found: 455.2562.

6-((2,5,5,8a-Tetramethyl-3,4,4a,5,6,7,8,8a-octahydronaphthalen-1-yl)methyl)benzo[d][1,3]dioxol-5-ol (26).

To a solution of **41** (2.1 g, 4.86 mmol) in dry methanol (20 mL) was added 10 % Pd/C (500 mg, 10 % mmol) and the reaction mixture was stirred at room temperature under hydrogen atmosphere (1.5 atm) for 1 h. Filtration and concentration yielded 1.62 g of **26** (97 %) as a colourless syrup.

[1'(2)*R*,2'*R*,4'a*R*,8'a*S*]-7-Formyl-5,6-methylenedioxy-3',4',4'a,5',6',7',8',8'a-octahydro-2',5',5',8'a-tetramethyl-spiro[benzofuran-2(3H),1'(2'H)-naphtalene] (42).

To a solution of **28** (420 mg, 1.22 mmol) in THF (12 mL), *n*-butyllithium (2.2 M in hexanes, 1.70 mL, 3.66 mmol) was added at -78 ºC under an argon atmosphere, and the reaction mixture was stirred at this temperature for 5 min. It was then allowed to warm to 5 ºC and subsequently cooled to -50 ºC. TMEDA (1.13 mL, 0.18 mmol) was added dropwise at -50 ºC and freshly distilled DMF (0.71 mL, 9.18 mmol) was also added dropwise to the resultant pale yellow solution. The mixture was stirred and allowed to warm to -40 ºC over 20 min, at which time TLC showed no starting material. Then, the reaction mixture was quenched with water (3 mL) and the solvent was removed. Et_2O - water (40: 10 mL) were added to the crude product and the phases were shaken and separated. The organic phase was washed with 2N HCl (3 x 10 mL), brine (2 x 10 mL), dried over anhydrous Na_2SO_4 and filtered. Removal of the solvent under reduced pressure afforded a crude product that was directly purified by flash chromatography (10% ether /hexanes) to give 322 mg of aldehyde **42** (72%) as a yellow syrup.

$[\alpha]_D^{25}$ = - 33.5 (c 20.2, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 10.26 (s, 1H, -CHO), 6.77 (s, 1H), 6.023 (s, 1H), 6.018 (s, 1H), 3.15 (d, *J* = 16.1 Hz, 1H), 2.74 (d, *J* = 16.1 Hz, 1H),

1.77 (tt, *J* = 12.1, 6.5 Hz, 1H), 1.66-1.45 (m, 5H), 1.43-1.24 (m, 5H), 1.14 (ddd, *J* = 13.4, 13.4, 3.7 Hz, 1H), 0.95 (s, 3H), 0.90 (s, 3H), 0.84 (s, 3H), 0.75 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 186.7 (-CHO), 157.3 (C), 145.5 (C), 141.4 (C), 118.9 (C), 110.7 (CH), 105.5 (C), 102.6 (CH_2), 99.1 (C), 46.7 (CH), 42.5 (C), 41.6 (CH_2), 37.2 (CH), 33.7 (C), 33.4 (CH_2), 33.2 (CH_3), 31.3 (CH_2), 31.1 (CH_2), 21.9 (CH_3), 21.3 (CH_2), 18.2 (CH_2), 16.1 (CH_3), 15.6 (CH_3). NOESY ($CDCl_3$, 500 MHz): Observed correlations: 3.15 (d, *J* = 16.1 Hz, 1H) with 0.95 (s, 3H); 2.74 (d, *J* = 16.1 Hz, 1H) with 0.75 (d, *J* = 6.5 Hz, 3H). IR (film): 1689, 1637, 1455, 1392, 1310, 1256, 1190, 1091, 1072, 1007, 968, 927, 760, 714, 630 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{23}H_{30}O_4Na$ ($M+Na^+$) 393.2042, found: 393.2046.

Corallidictyal D (2).

Anhydrous $AlCl_3$, (172 mg, 1.29 mmol, 3 equiv.) was added to a cold (- 40 ºC) solution of **42** (60 mg, 0.43 mmol) in dry dichloromethane (10 mL) under an atmosphere of Argon and the reaction mixture was stirred for 5 min, at which time TLC showed no starting material remaining. Then water (0.5 mL) was added and the organic solvent was removed under vacuum. The resulting crude product was dissolved in methanol (4 mL) and concentrated HCl (1 mL) was added, and the mixture was refluxed for 30 min (until none of the intermediate chloromethyl ether remained). The reaction mixture was allowed to cool to room temperature, the methanol was evaporated and the crude product was diluted with ether (50 mL), washed with water (3 x 20 mL) and brine (2 x 20 mL). The organic phase

was dried over anhydrous Na_2SO_4, filtered, and the solvent removed to give pure corallidictyal D **(2)** as a colorless oil (144 mg, 92%).

$[\alpha]_D^{25}$ = - 21.8 (c 14.8, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 11.09 (brs, 1H, -OH), 10.20 (s, 1H, -CHO), 6.93 (s, 1H), 5.09 (brs, 1H, -OH), 3.14 (d, *J* = 16.0 Hz, 1H), 2.73 (d, *J* = 16.0 Hz, 1H), 1.78 (tt, *J* = 12.4, 6.5 Hz, 1H), 1.67-1.53 (m, 3H), 1.48 (ddd, *J* = 16.3, 12.7, 3.1 Hz, 1H), 1.42-1.11 (m, 7H), 0.96 (s, 3H), 0.91 (s, 3H), 0.85 (s, 3H), 0.73 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 193.0 (-CHO), 157.0 (C), 146.3 (C), 137.0 (C), 119.5 (CH), 117.5 (C), 105.8 (C), 99.5 (C), 47.0 (CH), 42.6 (C), 41.8 (CH_2), 37.3 (CH), 33.7 (CH_2), 33.6 (CH_3), 33.4 (C), 31.5 (CH_2), 31.3 (CH_2), 22.0 (CH_3), 21.5 (CH_2), 18.4 (CH_2), 16.4 (CH_3), 15.8 (CH_3). NOESY ($CDCl_3$, 500 MHz): Observed correlations: 3.14 (d, *J* = 16.0 Hz, 1H) with 0.96 (s, 3H); 2.73 (d, *J* = 16.0 Hz, 1H) with 0.73 (d, *J* = 6.5 Hz, 3H). IR (film): 3565, 3419, 1652, 1634, 1470, 1386, 1332, 1299, 1255, 1236, 1213, 1109, 1069, 1032, 1010, 977, 936, 892, 856, 782, 752, 728, 667, 621 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{22}H_{30}O_4Na$ ($M+Na^+$) 381.2042, found: 381.2033.

^{1}H NMR (DMSO-d_6, 500 MHz) δ: 10.14 (s, 1H, -CHO), 6.90 (s, 1H), 3.10 (d, *J* = 16.2 Hz, 1H), 2.71 (d, *J* = 16.2 Hz, 1H), 1.77 (m, 1H), 1.60-1.05 (m, 11H), 0.93 (s, 3H), 0.88 (s, 3H), 0.82 (s, 3H), 0.67 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (DMSO-d_6, 125 MHz) δ: 191.9 (-CHO), 155.7 (C), 146.9 (C), 137.4 (C), 120.6 (CH), 116.8 (C), 106.1 (C), 98.2 (C), 46.1 (CH), 42.0 (C), 41.3 (CH_2), 36.4 (CH), 33.2 (CH_2), 32.9 (CH_3), 32.8 (C), 30.7 (CH_2), 30.7 (CH_2), 21.7 (CH_3), 20.9 (CH_2), 17.8 (CH_2), 15.7 (CH_3), 15.5 (CH_3).

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Supporting Information Available. ^{1}H NMR and ^{13}C NMR spectra for compounds **2**, **16-25**, **27-28**, **35-37** and **39-42,** NOESY for compounds **20** and **27,** and HSQC, HMBC and NOESY for compound **2.** This material is available free of charge via the internet at http://pubs.acs.org.

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