Exploration of High-Pressure Cycloadducts of Furans and Citraconic Anhydride as Precursors for CD-Ring Fragments of Paclitaxel and Its Analogues

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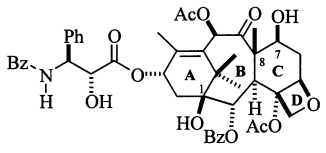
The high-pressure promoted Diels–Alder reactions between several furans and citraconic anhydride have been studied and the cycloadducts obtained have been explored in new straightforward routes to the CD-ring fragment of paclitaxel. The reaction between furan and citraconic anhydride afforded the *exo* cycloadduct diastereoselectively, whereas a variety of 2-substituted furans afforded approximate 1:1 mixtures of *exo* regioisomers. Separation of both regioisomers was accomplished after either diastereoselective esterification or regioselective reduction of the anhydride function. Ether cleavage of the bicyclic compounds by either high-pressure promoted ether cleavage or Boord elimination afforded several potential CD-ring precursors which can be used in the total synthesis of paclitaxel analogues.

Introduction

The cycloadducts of furan derivatives and maleic anhydride or dimethyl acetylenedicarboxylate have proved to be potential starting materials for the synthesis of the CD-ring fragment of the anticancer agent paclitaxel (Taxol®, **1**).[1][2][3] Vogel et al. and Sha et al., for example, prepared chiral CD-ring precursors **2** and **3** by treating (−)-furfuryl (1′*S*)-camphanate with maleic anhydride[2] and a chiral 2-siloxyfuran with dimethyl acetylenedicarboxylate[3], respectively.

Figure 1. Paclitaxel and CD-ring precursors **2** and **3**



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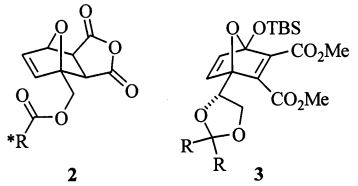

2 **3**

In all precursors reported so far, however, the angular methyl group (8-CH_3) which is present in paclitaxel is still lacking. This group may be important for the anticancer activity of paclitaxel by contributing to keeping the taxane skeleton in a so-called "inverted-cup" conformation.[4] It is generally assumed that this conformation is necessary for antineoplastic activity. Furthermore, the methyl group can control the regioselective coupling of an A-ring fragment to the CD-ring fragment in the total synthesis of paclitaxel derivatives.

We reasoned that cycloaddition reactions between furans and citraconic anhydride would directly lead to CD-ring precursors which contain this necessary methyl group. It is known from the literature that citraconic anhydride only reacts with furans at high pressures due to the strongly deactivating effect of the methyl group of citraconic anhydride. For example, Dauben et al. prepared the anthelminticum palasonin (**4**),[5] which was first isolated from the seeds of *Butea frondosa* by Raj and Kurup in 1967,[6] in two steps, a Diels−Alder reaction of furan with citraconic anhydride at 8 kbar followed by hydrogenation, in an overall yield of 74% (Scheme 1).[7] Without using high pressure, Meinwald et al. prepared palasonin (**4**) in twelve steps, starting with a thermal Diels−Alder reaction between furan and methoxycarbonyl maleic anhydride.[8] The methoxycarbonyl group proved to be necessary for sufficient activation of the dienophile at normal pressure.

In this report we describe the results of an exploratory study of the high-pressure promoted Diels−Alder reactions between several furans and citraconic anhydride. Special attention will be paid to the regio- and stereochemistry of these reactions. In addition, we report on the conversion of

[+] Both authors have equally contributed to this paper.

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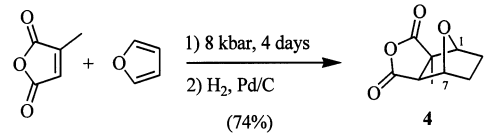
Scheme 1. High-pressure synthesis of palasonin (**4**)



the hydrogenated cycloadducts to potential CD-ring precursors of paclitaxel by way of selective reduction of the anhydride function and stereoselective opening of the ether bridge in the resulting lactones.

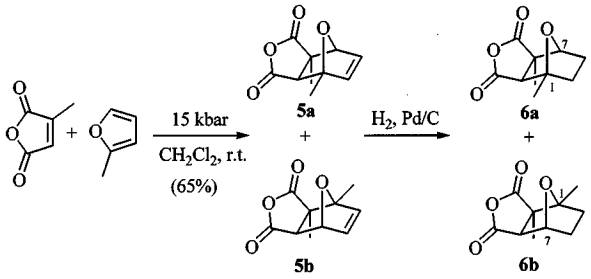
Results and Discussion

High-Pressure Promoted Diels–Alder Reaction of 2-Methylfuran

Being the simplest 2-substituted furan, 2-methylfuran was chosen the first diene to be used in the high-pressure promoted Diels–Alder reaction with citraconic anhydride. The reaction between 2-methylfuran and citraconic anhydride was performed at 15 kbar in dichloromethane and required 15 hours to reach a conversion of about 90%.[9][10] To avoid a retro Diels–Alder reaction at normal pressure, the reaction mixture was hydrogenated shortly after pressure release.[11]

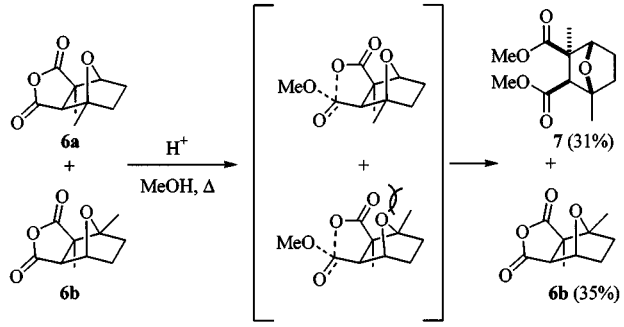
Two isomers were isolated after hydrogenation in an approximate 1:1 ratio. In the Diels–Alder reaction between citraconic anhydride and furan only the *exo* adduct is formed.[7] It was therefore assumed that the two isomers were *exo* regioisomers **5a** and **5b** (*exo* regioisomers **6a** and **6b** after hydrogenation; Scheme 2), which was confirmed by X-ray analysis (vide infra).

Scheme 2. High-pressure synthesis of anhydrides **6a**/**6b**



It proved to be impossible to separate isomers **6a** and **6b** by common methods. Alcoholysis of the anhydride function, possibly allowing separation of the two regioisomers, was therefore attempted. Surprisingly, only one of the two isomers was converted to its dimethyl ester after refluxing in a solution of 0.5% sulfuric acid in methanol for two days (Scheme 3). Although the dimethyl ester and unreacted anhydride **6a** or **6b** were separated, it proved impossible to determine which of the two anhydrides had reacted on the basis of simple ^{1}H NMR, because both 2-H in **6a** and 6-H in **6b** gave singlet signals. The *exo* configuration causes the dihedral angle between 6-H and 7-H in **6b** to be approximately 90°.

Scheme 3. Selective anhydride opening of **6a**/**6b**



The structure of dimethyl ester **7** was unambiguously elucidated by X-ray analysis. An ORTEP drawing[12] of the crystal structure of dimethyl ester **7** is depicted in Figure 2. The relative orientation of both methyl groups in dimethyl ester **7** clearly indicates that isomer **6a** has reacted with methanol.

The completely specific anhydride opening of isomer **6a** is uncommon. It is most probable that methanol attacks the less hindered carbonyl group of the anhydride function in both isomers, which leads to a tetrahedral intermediate. Ring opening of this intermediate may be hindered in case of isomer **6b** due to steric interactions between the 1-methyl group and the leaving carboxylate group (Scheme 3).[13]

Selective Reduction of the Cyclic Anhydride Function

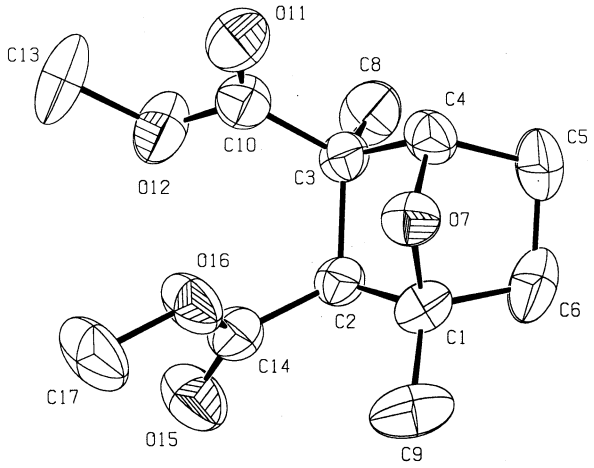
The two carbonyl groups in the hydrogenated adducts were expected to differ in reactivity towards nucleophiles due to the close proximity of the *endo*-methyl group to one of the carbonyl groups. A difference in reactivity is necessary for selective coupling to the AB part of the taxane skeleton. As a first approach to explore selective reactions of the hydrogenated adducts **4** and **6b**, reduction of the anhydride function with sodium tetrahydroborate was studied. In general, the more electron-rich, i.e. the more sterically hindered, carbonyl group is reduced. Some tricyclic anhydrides, however, are reduced at the less sterically hindered carbonyl group.[14]

Reaction of palasonin (**4**) with sodium tetrahydroborate resulted in reduction of the less sterically hindered carbonyl group (lactone **8**). In the same way, lactone **9** was prepared by reduction of anhydride **6b**. The structure of lactone **9** was confirmed by X-ray analysis of crystalline lactone **9**. An ORTEP drawing[12] of the crystal structure of lactone **9**, clearly showing the methyl group at the α-position of the carbonyl group, is depicted in Figure 2.

2-Alkoxymethylfurans and 2-Acyloxymethylfurans

The results of the Diels–Alder reactions between citraconic anhydride and several 2-alkoxymethylfurans and 2-acyloxymethylfurans are summarised in Table 1. All reac-

Figure 2. ORTEP drawings[12] of the crystal structures of dimethyl ester **7** and lactone **9**; hydrogen atoms have been omitted for clarity



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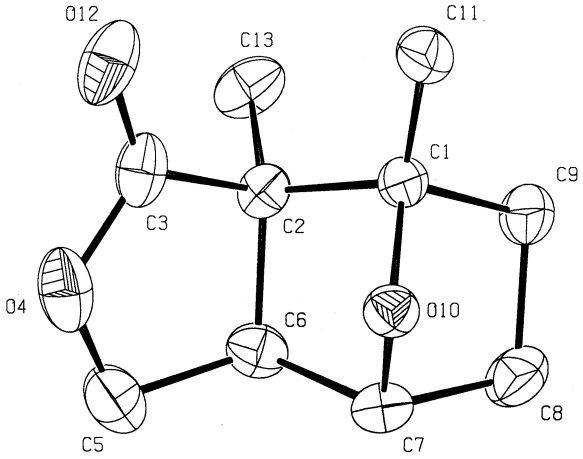

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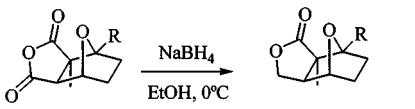
Scheme 4. Selective reduction of anhydrides **4** and **6b**



4: R = H
6b: R = Me

8: R = H (92%)
9: R = Me (82%)

tions were carried out at a pressure of 15 kbar.[9] To avoid retro Diels–Alder reactions, the crude reaction mixtures were hydrogenated shortly after pressure release.[11] Again, mixtures of *exo* regioisomers were obtained. Structures **a** and **b** were assigned on the basis of similarities between the ^{1}H-NMR spectra of compounds **15**–**17** and that of the mixture of **6a** and **6b**. Only after opening of the ether bridge, however, were we able to determine the constitution of both isomeric series with absolute certainty (vide infra).

The reactivity of the furans is dependent on the substituent R. For example, no Diels–Alder reaction took place with furan **10** which has a strongly electron-withdrawing substituent. Furthermore, the cycloaddition reactions between furans **11**–**13** and citraconic anhydride required a reaction time of 60 hours to achieve maximum conversion[10], which is 4 times more than that required for the cycloaddition reaction between 2-methylfuran and citraconic anhydride. The lower reactivity of furans **11**–**13** compared to 2-methylfuran is probably due to the presence of less electron-donating substituents. The lower rate of the Diels–Alder reaction led to a decrease in reaction yield, because polymerisation reactions of the furan derivatives became more important side reactions.

The small electronic differences between the substituents caused only minor differences in the ratio of both *exo* regioisomers, the average ratio of isomers **a** and **b** being close to 1:1 in all cases.

It proved impossible to separate regioisomers **a** and **b** by common methods. Reduction of **15**–**17** with sodium tetrahydroborate in ethanol, however, afforded lactones **18**–**20** which were easily separated by column chromatography. In each case, the less sterically hindered carbonyl group of the cyclic anhydride function was regioselectively reduced.

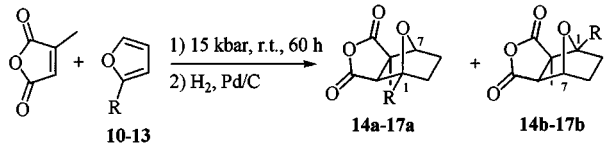
Opening of the Ether Bridge

In order to obtain paclitaxel CD-ring precursors, the ether bridge in tricyclic lactones **8**, **9**, and **18**–**20** had to be opened regioselectively. Several methods for opening of the ether bridge in 7-oxabicyclo[2.2.1]heptanes have been reported.[15][16][17][18][19] Some methods involve S_N2'-like substitutions[15], others involve ether cleavage in either (Lewis) acid[18] or basic[19] medium.

When Lewis acid catalysed ether cleavage is carried out at normal pressure, forcing conditions are required.[20] However, cyclic ethers can easily be cleaved by acyl halides at high pressures. These reactions involve simultaneous bond formation and ionisation processes and are therefore strongly promoted by high pressure.[21] We rationalised that ether cleavage in 7-oxabicyclo[2.2.1]heptanes could be achieved by treating them under high pressure with acylium ion generating reactants, e.g. acetyl halides or mixed anhydrides such as acetic trifluoroacetic anhydride. The regioselectivity in this type of reactions is controlled by ring opening of the oxonium ion to the most stable carbocation, which is then further transformed into either a substitution or elimination product.

First, we studied the ether cleavage in lactone **8** at 15 kbar, using acetyl bromide as the acylium ion donor. The reaction proceeded regio- and stereoselectively, affording only bromide **21**. The *cis* relationship between the acetate group and the bromo atom was tentatively assigned by assuming that compound **21** is formed by collapse of intermediate **A** (Scheme 6). Reaction of lactone **8** with acetic-trifluoroacetic anhydride afforded a mixture of **22** and **23**

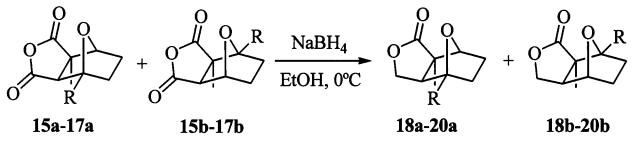
Table 1. High-pressure promoted synthesis of anhydrides **14**−**17**



R	furan	DA reaction conditions	product	**a**/**b**[a]	yield[b] (%)
C(O)OEt	**10**	15 kbar, CH_2Cl_2, 60 h	**14**	−	0
$CH_2OC(O)C(CH_3)_3$	**11**	15 kbar, CH_2Cl_2, 60 h	**15**	1:1	54
CH_2OAc	**12**	15 kbar, CH_2Cl_2, 60 h	**16**	5:6	59
CH_2OCH_2Ph	**13**	15 kbar, CH_2Cl_2, 60 h	**17**	7:5	31

[a] The ratio of isomers **a** and **b** was determined from the relative intensities of the signals of 2-H (isomer **a**) and 6-H (isomer **b**) in the ^{1}H-NMR spectrum of the crude reaction mixture. − [b] Crude yield after distillation.

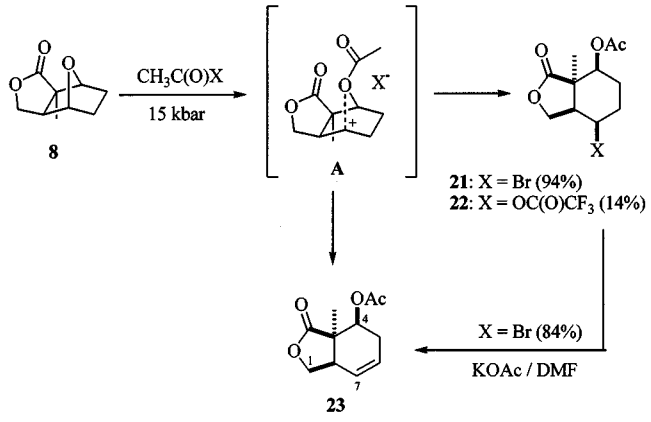
Scheme 5. Reduction of anhydrides **15**−**17** with $NaBH_4$



18: R = $CH_2OC(O)C(CH_3)_3$
19: R = CH_2OAc
20: R = CH_2OCH_2Ph

in a ratio varying from 2:1 ($CHCl_3$, 1,2-dichloroethane) to 1:2 (CH_3CN). Separation of this mixture proved difficult. Compound **22** was obtained pure after crystallisation from hexane/ethyl acetate in a yield of 14%. Bicyclic alkene **23** can, however, easily be obtained pure by treating bromide **21** with potassium acetate in DMF.

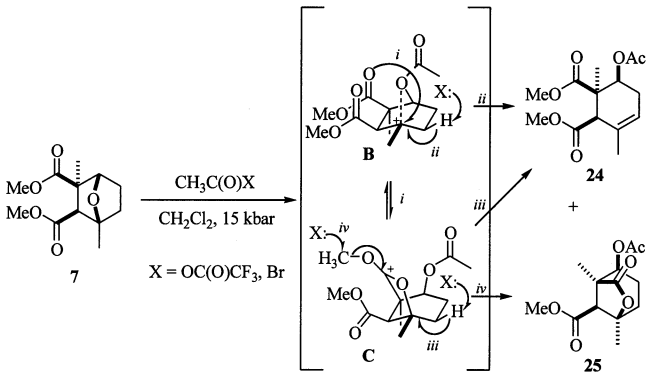
Scheme 6. High-pressure promoted ether cleavage of lactone **8**



Formation of **23** when acetic trifluoroacetic anhydride is used as the acetylating agent is in full accordance with the fact that a trifluoroacetate ion is harder than a bromide ion.

Ether cleavage of dimethyl ester **7** at a pressure of 15 kbar using acetic trifluoroacetic anhydride as the acetylating agent proceeded smoothly and afforded two products, cyclohexene **24** and lactone **25**, in yields of 68% and 22%, respectively (Scheme 7). When the reaction time was prolonged from 3 to 24 hours, the product ratio did not change significantly. This seemed to imply that lactone **25** was not formed from cyclohexene **24**, but directly from dimethyl ester **7**. No product was isolated with a double bond in conjugation with the carbonyl group. This may indicate that proton abstraction from the intermediate cation **B** or **C** occurs by X^- that is still located on the side of the acetyl group.

Scheme 7. High-pressure promoted ether cleavage of dimethyl ester **7**



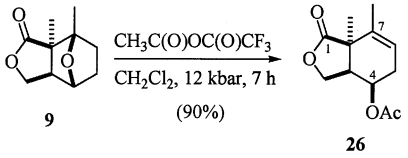
As the ester group and the "ether bridge" are on the same side of the six-membered ring, lactone **25** is most probably formed by substitution of the "ether bridge" with the ester group by an S_N1 mechanism, followed by nucleophilic attack of X^- on the methyl group of the dialkoxy carbocation **C** (step *i*, *iv*). Cyclohexene **24** can be formed by elimination of a proton from either intermediate **B** (step *ii*) or intermediate **C** (step *iii*).

Due to the higher stability of a tertiary carbocation in comparison with a secondary one, ether cleavage in dimethyl ester **7** occurs with complete regioselectivity.

When acetyl bromide was used as the acylium ion donor, only lactone **25** was isolated, in agreement again with the fact that a bromide ion is a softer base and a better nucleophile than trifluoroacetate.

High-pressure promoted ether cleavage of lactone **9** using acetic trifluoroacetic anhydride as the acetylating agent also proceeded with complete regioselectivity, affording cyclohexene **26** in a yield of 90%.

Scheme 8. High-pressure promoted ether cleavage of lactone **9**

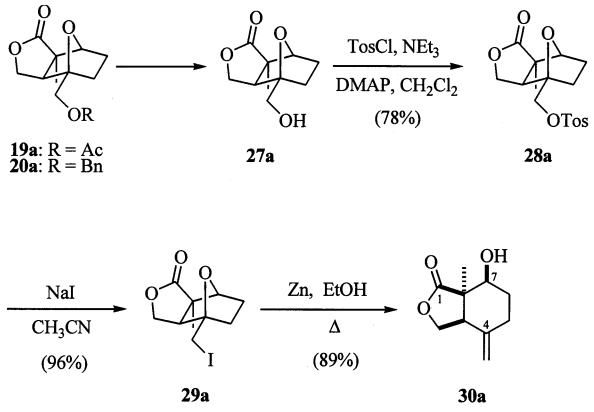


9 **26**

In general, high-pressure promoted ring opening of compounds **18**−**20** using acylium ion donating agents was less selective. For example, treatment of compound **19b** with acetyl bromide at 15 kbar afforded a mixture of at least three compounds, while ether cleavage with acetic trifluoroacetic anhydride proceeded only at 50°C and 15 kbar in low yield.

Due to diminished selectivity in the high-pressure promoted ether cleavage, ether opening of lactones **19a** and **20a** was accomplished by a reaction sequence first introduced by Yadav et al. for related compounds (Scheme 9).[1b]

Scheme 9. Conversion of lactones **19a**/**20a** to CD-ring precursor **30a**

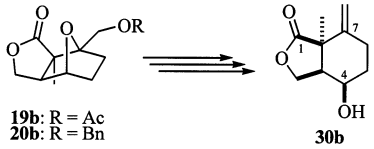


The protected alcohol group in lactone **19a** was deprotected under basic conditions ($MeOH/H_2O/Na_2CO_3$) in a yield of 92%. Lactone **20a** was deprotected at 40 bar hydrogen pressure using palladium on activated carbon as a catalyst, affording alcohol **27a** in quantitative yield.

The primary alcohol group of alcohol **27a** was then transformed into a good leaving group using tosyl chloride in CH_2Cl_2, affording **28a** in a yield of 78%. The tosylate group was then substituted with iodide. The reaction was carried out in acetonitrile using 3 equivalents of NaI, and afforded iodide **29a** in a yield of 96%. Finally, iodide **29a** was converted to **30a** using Boord conditions.[22] The Boord reaction is generally applied to effect elimination of ROX with, for instance, zinc as the reducing agent.

The reaction sequence depicted in Scheme 9 was also carried out with lactones **19b** and **20b** resulting in the formation of alcohol **30b** in overall yields of 43% and 45%, respectively (Scheme 10). In general, longer reaction times and/or more equivalents of reagents were required to complete the reactions. The *endo*-methyl groups in lactones **19b** and **20b** are closer to the reaction centre than in lactones **19a** and **20a**, increasing steric hindrance. It was especially in the preparation of **29b** from **28b** that significant changes in reaction time and conditions were required.

Scheme 10. Conversion of lactones **19b**/**20b** to **30b**



The ^{1}H-NMR spectra of alcohols **30a** and **30b** allowed the determination of which Diels−Alder regioisomer they originated from, as the opening of the ether bridge now caused the ^3J coupling between 3a-H and 4-H in alcohol **30b** to be > 0 Hz.

Conclusions

Straightforward syntheses have been developed for bicyclic alkene **23**, cyclohexene **24**, and alcohol **30a** which can be applied as potential precursors in the total synthesis of paclitaxel and paclitaxel analogues. The application of high pressure has played a key role in these syntheses, because the cycloaddition reactions as well as the ether cleavage in the syntheses of compounds **23** and **24** have been performed at high pressures. Bicyclic alkene **23**, which can be prepared from citraconic anhydride and furan in 5 steps in an overall yield of 54%, may be an appropriate starting material for the syntheses of paclitaxel analogues with a modified CD part. Although cyclohexene **24** can be obtained in only four steps from 2-methylfuran and citraconic anhydride, the overall yield is much lower due to the formation of regioisomers in the cycloaddition reaction.

The double bond in each precursor allows the construction of the oxetane ring or other four-membered rings, whereas the lactone ring allows the regioselective attachment of an AB part. The angular methyl group present in paclitaxel is also present in precursors **23**, **24**, and **30a**. The methyl group and the hydroxy group are still oriented *trans* in these precursors, while oriented *cis* in paclitaxel. However, inversion of the hydroxy function in taxanes can easily be achieved under basic or acidic conditions.[23]

In most total syntheses of paclitaxel, the oxetane ring is constructed near the end of the synthesis to prevent premature decomposition.[24] This supports the fact that precursors **23**, **24**, and **30a** can be used directly in the construction of the taxane part of paclitaxel and paclitaxel analogues. We are currently exploring precursors **23**, **24**, and **30a** in a straightforward synthesis of paclitaxel analogues.

Experimental Section

General Remarks: When necessary, solvents were dried and distilled following standard procedures. The high-pressure apparatus used has been described before.[25] Reactions were carried out in sealed 15-ml Teflon vessels. 5-*tert*-Butyl-4-hydroxy-2-methylphenyl sulfide was used as radical inhibitor in all high-pressure reactions. − Analytical TLC: Merck glass-backed silica gel 60 F_{254} plates.

− Column chromatography: Merck silica gel 60, 0.063−0.200 mm (70−230 mesh) or 60 H, 0.005−0.040 mm. − IR: Bio-Rad FTS-25 single-beam spectrometer. − NMR: Bruker AC-100, Bruker AC-300 and Bruker AM-400, $CDCl_3$ as solvent, TMS as internal standard. − MS: Double-focusing VG7070E spectrometer (EI, FAB) and Varian Saturn GC/MS.

Crystallographic Data of Compounds **7** *and* **9**: J. M. M. Smits, R. W. M. Aben, P. H. Beusker, R. de Gelder, to be published in *J. Chem. Crystallogr.*

1,6-Dimethyl-4,10-dioxatricyclo[5.2.1.0^{2,6}]decane-3,5-dione (**6a**) *and 1,2-Dimethyl-4,10-dioxatricyclo[5.2.1.0^{2,6}]decane-3,5-dione* (**6b**): A solution of 2-methylfuran (3.3 g, 40.2 mmol), citraconic anhydride (3.0 g, 27 mmol) and radical inhibitor (10 mg, 0.028 mmol) in CH_2Cl_2 (9 ml) was kept at 15 kbar for 16 h. The reaction mixture was depressurised and diluted with ethyl acetate/ethanol (20 ml, 2:1 v/v) and hydrogenated at 40 psi ≙ 2.7 bar hydrogen pressure over 10% palladium on activated coal for 3 h. After removal of the solvent, the crude reaction mixture was distilled by bulb-to-bulb distillation (130−140°C/0.5 Torr), affording 3.45 g of **6a**/**6b** (65%) as a white solid. This mixture was used as such in the next step.

Dimethyl 1,3-Dimethyl-7-oxabicyclo[2.2.1]heptane-2,3-dicarboxylate (**7**) *and 1,2-Dimethyl-4,10-dioxatricyclo[5.2.1.0^{2,6}]decane-3,5-dione* (**6b**): A solution of **6a**/**6b** (3 g, 15.3 mmol) in 0.5% sulfuric acid in methanol (50 ml) was refluxed for 2 d. The solution was then cooled to room temperature, neutralised with solid $NaHCO_3$ and filtered. The solvent was evaporated in vacuo and the residue was distilled by bulb-to-bulb distillation (125−130°C/0.5 Torr). Anhydride **6b** was obtained by crystallisation of the crude distillate from consecutively diisopropyl ether and *n*-hexane/ethyl acetate (1:1 v/v) in a yield of 1.05 g (35%). The mother liquor containing dimethyl ester **7** was concentrated in vacuo and the residue was purified by fractional distillation (102°C/0.5 Torr), affording dimethyl ester **7** (1.14 g, 31%).

6b: Colourless crystals, m.p. 159°C. − IR (KBr): $\tilde{\nu}$ = 1771 cm^{-1}, 1849 (C=O). − ^{1}H NMR (400 MHz): δ = 4.81 (d, $J_{7\text{-}8}$ = 5.31 Hz, 1 H, 7-H), 2.80 (s, 1 H, 6-H), 2.00−2.09 (m, 2 H, 8/9-H), 1.67 (m, 1 H, 8/9-H), 1.44−1.63 (m, 1 H, 8/9-H), 1.56 (s, 3 H, 1-CH_3), 1.44 (s, 3 H, 2-CH_3). − ^{13}C NMR (100 MHz): δ = 174.24 [*C*(O)OR], 171.371 [*C*(O)OR], 89.37 (C-1) 79.97 (C-7), 60.00 (C-2), 57.69 (C-6), 31.06 (C-9), 29.80 (C-8), 16.93 (1-*C*H$_3$), 16.33 (2-*C*H$_3$). − MS; *m/z* (%): 197 (37.1) [M$^+$ + 1], 168 (13.4), 151 (34.03), 96 (100.0). − $C_{10}H_{12}O_4$ (196.2): calcd. C 64.27, H 7.19; found C 64.14, H 7.26.

7: Colourless crystals, m.p. 46−48°C. − ^{1}H NMR (400 MHz): δ = 4.97 (d, $J_{4\text{-}5}$ = 4.99 Hz, 1 H, 4-H), 3.67 [s, 3 H, C(O)OCH_3], 3.66 [s, 3 H, C(O)OCH_3], 2.58 (s, 1 H, 2-H), 1.82-1.92 (m, 2 H, 5/6-H), 1.60−1.69 (m, 2 H, 5/6-H), 1.42 (s, 3 H, 1-CH_3), 1.42 (s, 3 H, 3-CH_3). − $C_{12}H_{18}O_5$ (242.3): calcd. C 59.49, H 7.49; found C 59.50, H 7.51.

2-Methyl-4,10-dioxatricyclo[5.2.1.0^{2,6}]decan-3-one (**8**): To a solution of palasonin[7] (**4**) (1.0 g, 5.5 mmol) in 25 ml of ethanol which was cooled to 0°C $NaBH_4$ (0.23 g, 6.0 mmol) was added in small portions. The reaction mixture was kept at 0°C for half an hour and was then stirred at room temperature for 2 h. The solution was acidified with a 1 N HCl solution. The solvent was evaporated and the residue dissolved in dichloromethane. The solution was washed with a saturated $NaHCO_3$ solution, dried with Na_2SO_4, and concentrated in vacuo, affording lactone **8** (850 mg, 5.05 mmol, 92%) as a white amorphous powder, m. p.: 77−78°C. − IR (KBr): $\tilde{\nu}$ = 1757 cm^{-1} (C=O). − ^{1}H NMR (400 MHz): δ = 4.59 (d, $J_{7\text{-}8}$ = 4.96 Hz, 1 H, H$_7$), 4.48 (d, $J_{1\text{-}9}$ = 5.31 Hz, 1 H, H$_1$), 4.40 (pseudo-t, *J* = 9.1 Hz, 1 H, H$_5$), 4.11 (dd, J_{gem} = 9.54 Hz, $J_{5'\text{-}6}$ = 3.19 Hz, 1 H, H$_{5'}$), 2.19 (dd, $J_{6\text{-}5}$ = 8.57 Hz, $J_{6\text{-}5'}$ = 3.19 Hz, 1 H, H$_6$), 1.87−1.93 (m, 1 H, H$_{8/9}$), 1.67−1.80 (m, 2 H, H$_{8/9}$), 1.35−1.52 (m, 1 H, H$_{8/9}$), 1.35 (s, 3 H, 2-CH_3). − ^{13}C NMR (100 MHz): δ = 181.30 (C-3), 83.99 (C-1), 82.74 (C-7), 71.01 (C-5), 53.13 (C$_2$), 50.00 (C-6), 27.65 (C-8), 23.96 (C-9), 17.35 (2-*C*H$_3$). − MS; *m/z* (%): 169 (98.5) [M$^+$ + 1], 168 (75.5) [M$^+$], 150 (21.1), 138 (9.5), 39 (100.0). − $C_9H_{12}O_3$ (168.2): calcd. C 64.27, H 7.19; found C 64.32, H 7.05.

1,2-Dimethyl-4,10-dioxatricyclo[5.2.1.0^{2,6}]decan-3-one (**9**): To a solution of anhydride **6b** (3 g, 15.3 mmol) in ethanol (80 ml) which was cooled to 0°C $NaBH_4$ (0.64 g, 16.8 mmol) was added in small portions. The reaction mixture was kept at 0°C for 0.5 h and was then stirred at room temperature for 2.5 h. The solution was acidified with a 1 N HCl solution. The solvent was evaporated and the residue was dissolved in dichloromethane. The solution was washed with a saturated $NaHCO_3$ solution, dried with Na_2SO_4, and concentrated in vacuo. Recrystallisation of the crude product from diisopropyl ether afforded lactone **9** (2.29 g, 82%) as colourless crystals, m. p. 88°C. − IR (KBr): $\tilde{\nu}$ = 1758 cm^{-1} (C=O). − ^{1}H NMR (400 MHz): δ = 4.38 (pseudo-t, *J* = 9.2 Hz, 1 H, 5-H), 4.35 (d, $J_{7\text{-}8}$ = 5.50 Hz, 1 H, 7-H), 4.02 (dd, J_{gem} = 9.39 Hz, $J_{5'\text{-}6}$ = 3.79 Hz, 1 H, 5′-H), 2.31 (dd, $J_{6\text{-}5}$ = 3.79 Hz, $J_{6\text{-}5'}$ = 8.91 Hz, 1 H, 6-H), 2.04 (m, 1 H, 9$_{endo}$-H), 1.91 (m, 1 H, 8$_{exo}$-H), 1.55 (m, 1 H, 8$_{endo}$-H), 1.44 (m, 1 H, 9$_{exo}$-H), 1.52 (s, 3 H, 1-CH_3), 1.33 (s, 3 H, 2-CH_3). − ^{13}C NMR (100 MHz): δ = 179.65 (C-3), 88.30 (C-1), 82.46 (C-7), 70.66 (C-5), 53.70 (C-2), 51.55 (C-6), 31.78 (C-9), 29.51 (C-8), 18.58 (1-*C*H$_3$), 16.16 (2-*C*H$_3$). − MS; *m/z* (%): 183 (14.4) [M$^+$ + 1], 43 (100.0). − Peak match: calcd. 182.0943; found 182.0943 ± 0.0011. − $C_{10}H_{14}O_3$ (182.2): calcd. C 65.92, H 7.74; found C 65.59, H 7.73.

General Procedure for the Synthesis of 1-Substituted 2(6)-Methyl-4,10-dioxatricyclo[5.2.1.0^{2,6}]decane-3,5-diones **14**−**17**: A mixture of 2-alkoxyfuran (32 mmol), citraconic anhydride (3.0 g, 26.8 mmol) and radical inhibitor (10 mg, 0.028 mmol) was diluted up to 15 ml with dichloromethane. The reaction mixture was kept at 15 kbar for 60 h, depressurised, diluted with ethyl acetate/ethanol (20 ml, 2:1 v/v) and hydrogenated at 40 psi ≙ 2.7 bar over 10% palladium on activated coal for 3 h. The reaction mixture was filtered and concentrated in vacuo. The residue was distilled by bulb-to-bulb distillation (**15**: 165−175°C/0.2 Torr; **16**: 180−185°C/0.8 Torr; **17**: 175−185°C/0.3 Torr), affording a crude product mixture which was used as such in the next reaction step.

{2(6)-Methyl-3,5-dioxo-4,10-dioxatricyclo[5.2.1.0^{2,6}]dec-1-yl}-methyl Acetate (**16a**/**16b**): White solid, yield 59%. − IR (KBr): $\tilde{\nu}$ = 1740 cm^{-1}, 1774, 1850 (C=O). − ^{1}H NMR (300 MHz)[26]: isomer **a**: δ = 4.75 (d, $J_{7\text{-}8}$ = 2.7 Hz, 1 H, 7-H), 4.48 (s, 2 H, 1-CH_2OR), 2.73 (s, 1 H, 2-H), 2.08 [s, 3 H, 1-CH$_2$OC(O)CH_3], 1.60−2.05 (m, 4 H, 8-H/9-H), 1.46 (s, 3 H, 6-CH_3); isomer **b**: δ = 4.89 (d, $J_{7\text{-}8}$ = 5.36 Hz, 1 H, 7-H), 4.57 (d, J_{gem} = 12.63 Hz, 1 H, 1-C*H*HOR), 4.44 (d, J_{gem} = 12.7 Hz, 1 H, 1-CH*H*OR), 2.82 (s, 1 H, 6-H), 2.10 [s, 3 H, 1-CH$_2$OC(O)CH_3], 1.60−2.05 (m, 4 H, 8-H/9-H), 1.52 (s, 3 H, 2-CH_3). − MS; *m/z* (%): 255 (0.8) [M$^+$ + 1], 212 (9.5), 194 (10.1), 43 (100.0). − Peak match: calcd. 254.0790; found 254.0791 ± 0.0012.

1-[(Benzyloxy)methyl]-2(6)-methyl-4,10-dioxatricyclo-[5.2.1.0^{2,6}]decane-3,5-dione (**17a**/**17b**): White solid, yield 31%. − IR (KBr): $\tilde{\nu}$ = 1776 cm^{-1}, 1841 (C=O). − ^{1}H NMR (100 MHz)[26]: isomer **a**: δ = 7.34 (br. s, 5 H, H$_{Ph}$), 4.75 (d, 1 H, 7-H), 4.60 (s, 2 H, Ph-CH_2OR), 3.88 (d, J_{gem} = 12 Hz, 1 H, 1-C*H*HOR), 3.79 (d, J_{gem} = 12 Hz, 1 H, 1-CH*H*OR), 2.72 (s, 1 H, 2-H), 1.45−2.20 (m, 4 H, 8-H/9-H), 1.45 (s, 3 H, 6-CH_3); isomer **b**: δ = 7.34 (br. s, 5 H, H$_{Ph}$), 4.89 (d, 1 H, 7-H), 4.60 (s, 2 H, Ph-CH_2OR), 3.94 (d,

J_{gem} = 11 Hz, 1 H, 1-C*H*HOR), 3.85 (d, J_{gem} = 11 Hz, 1 H, 1-CH*H*OR), 2.77 (s, 1 H, 6-H), 1.45−2.20 (m, 4 H, 8-H/9-H), 1.50 (s, 3 H, 2-CH_3). − MS; *m/z* (%): 303 (11.8) [M^+ + 1], 284 (8.5), 195 (20.1), 91 (100.0). − Peak match: calcd. 302.1154, found 302.1156 ± 0.0012.

General Procedure for the Reduction of 1-(Alkoxymethyl)-2(6)-methyl-4,10-dioxatricyclo[5.2.1.0^{2,6}]decane-3,5-diones and {2(6)-Methyl-3,5-dioxo-4,10-dioxatricyclo[5.2.1.0^{2,6}]dec-1-yl}methyl Alkanoates **15**−**17** *with* $NaBH_4$: To a solution of **15a**/**15b**, **16a**/**16b**, or **17a**/**17b** (10 mmol) in ethanol (80 ml) which was cooled to 0°C $NaBH_4$ (0.42 g, 11 mmol) was added. The reaction mixture was kept at 0°C for 0.5 h and was then stirred at room temperature for 2.5 h. The solution was acidified with a 1 N HCl solution. The solvent was evaporated and the residue was dissolved in dichloromethane. The solution was washed with a saturated $NaHCO_3$ solution, dried with Na_2SO_4, and concentrated in vacuo. Lactones **a** and **b** were separated by column chromatography.

{6-Methyl-5-oxo-4,10-dioxatricyclo[5.2.1.0^{2,6}]dec-1-yl}methyl Pivalate (**18a**): White solid, yield 19%. − M.p. 103°C. − ^{1}H NMR (300 MHz): δ = 4.59 (d, $J_{7\text{-}8}$ = 4.63 Hz, 1 H, 7-H), 4.53 (d, J_{gem} = 11.77 Hz, 1 H, 1-C*H*HOR), 4.36 (dd, J_{gem} = 10.8 Hz, $J_{3\text{-}2}$ = 3.0 Hz, 1 H, 3-H), 4.32 (d, J_{gem} = 11.7 Hz, 1 H, 1-CH*H*OR), 4.25 (pseudo-t, J_{gem} = 9.3 Hz, $J_{3'\text{-}2}$ = 9.3 Hz, 1 H, 3′-H), 2.23 (dd, $J_{2\text{-}3}$ = 3.05 Hz, $J_{2\text{-}3'}$ = 8.15 Hz, 1 H, 2-H), 1.55−2.00 (m, 4 H, 8/9-H), 1.35 (s, 3 H, 6-CH_3), 1.20 (s, 9 H, *tert*-butyl). − MS; *m/z* (%): 282 (1.1) [M^+], 267 (1.0), 198 (4.1), 184 (14.1), 57 (100.0). − $C_{15}H_{22}O_5$ (282.3): calcd. C 63.81, H 7.85; found C 64.00, H 7.83.

{2-Methyl-3-oxo-4,10-dioxatricyclo[5.2.1.0^{2,6}]dec-1-yl}methyl Pivalate (**18b**): White solid, yield 22%. − M.p. 119°C. − ^{1}H NMR (300 MHz): δ = 4.62 (d, J_{gem} = 12.46 Hz, 1 H, 1-C*H*HOR), 4.45 (d, J_{gem} = 12.6 Hz, 1 H, 1-CH*H*OR), 4.43 (d, $J_{7\text{-}8}$ = 5.1 Hz, 1 H, 7-H), 4.40 (pseudo-t, J = 9.0 Hz, 1 H, 5-H), 4.08 (dd, J_{gem} = 9.43 Hz, $J_{5'\text{-}6}$ = 3.76 Hz, 1 H, 5′-H), 2.36 (dd, $J_{6\text{-}5}$ = 8.71 Hz, $J_{6\text{-}5'}$ = 3.79 Hz, 6-H), 1.90−1.95 (m, 2 H, 8/9-H), 1.56−1.72 (m, 2 H, 8/9-H), 1.44 (s, 3 H, 2-CH_3), 1.22 (s, 9 H, *tert*-butyl). − MS; *m/z* (%): 282 (2.6) [M^+], 198 (32.4), 180 (6.7), 57 (100.0). − $C_{15}H_{22}O_5$ (282.3): calcd. C 63.81, H 7.85; found C 63.79, H 7.77.

{6-Methyl-5-oxo-4,10-dioxatricyclo[5.2.1.0^{2,6}]dec-1-yl}methyl Acetate (**19a**): White solid, yield 22%. − M.p. 81°C. − IR (KBr): $\tilde{\nu}$ = 1739 cm^{-1}, 1768 (C=O). − ^{1}H NMR (400 MHz): δ = 4.61 (d, $J_{7\text{-}8}$ = 4.75 Hz, 1 H, 7-H), 4.53 (d, J_{gem} = 11.91 Hz, 1 H, 1-C*H*HOR), 4.36 (d, J_{gem} = 11.4 Hz, 1 H, 1-CH*H*OR), 4.36 (dd, J_{gem} = 10.1 Hz, $J_{3\text{-}2}$ = 8.20 Hz, 1 H, 3-H), 4.26 (dd, J_{gem} = 10.40 Hz, $J_{3'\text{-}2}$ = 8.20 Hz, 1 H, 3′-H), 2.28 (dd, $J_{2\text{-}3}$ = 2.99 Hz, $J_{2\text{-}3'}$ = 8.20 Hz, 1 H, 2-H), 2.10 [s, 3 H, OC(O)CH_3], 2.00 (m, 1 H, 8/9-H), 1.76−1.90 (m, 2 H, 8/9-H), 1.57 (m, 1 H, 8/9-H), 1.37 (s, 3 H, 6-CH_3). − ^{13}C NMR (25 MHz): δ = 180.82 (C-5), 170.53 [O*C*(O)CH$_3$], 87.24 (C-1), 83.37 (C-7), 66.63 (1-*C*H$_2$OAc), 63.07 (C-3), 53.95 (C-6), 51.73 (C-2), 31.79 (C-9), 25.30 (C-8), 20.77 [OC(O)*C*H$_3$], 17.65 (6-*C*H$_3$). − MS; *m/z* (%): 240 (15.3) [M^+], 198 (3.5), 181 (6.5), 43 (100.0). − $C_{12}H_{16}O_5$ (240.3): calcd. C 59.64, H 6.64; found C 59.99, H 6.77.

{2-Methyl-3-oxo-4,10-dioxatricyclo[5.2.1.0^{2,6}]dec-1-yl}methyl Acetate (**19b**): White solid, yield 27%. − M.p. 99°C. − IR (KBr): $\tilde{\nu}$ = 1740 cm^{-1}, 1759 (C=O). − ^{1}H NMR (400 MHz): δ = 4.63 (d, J_{gem} = 12.69 Hz, 1 H, 1-CH*H*OAc), 4.47 (d, J_{gem} = 12.65 Hz, 1 H, 1-C*H*HOAc), 4.45 (d, $J_{7\text{-}8}$ = 5.09 Hz, 1 H, 7-H), 4.42 (pseudo-t, J = 9.2 Hz, 1 H, 5-H), 4.10 (dd, J_{gem} = 9.47 Hz, $J_{5'\text{-}6}$ = 3.86 Hz, 1 H, 5′-H), 2.38 (dd, $J_{6\text{-}5}$ = 8.91 Hz, $J_{6\text{-}5'}$ = 3.87 Hz, 1 H, 6-H), 2.11 [s, 3 H, OC(O)CH_3], 1.90−1.98 (m, 2 H, 8/9-H), 1.74 (m, 1 H, 8/9-H), 1.61 (m, 1 H, 8/9-H), 1.43 (s, 3 H, 2-CH_3). − ^{13}C NMR (100 MHz): δ = 178.77 (C-3), 170.38 [O*C*(O)CH$_3$], 88.39 (C-1), 82.99 (C-7), 70.77 (C-5), 61.82 (1-*C*H$_2$OAc), 54.07 (C-2), 51.73 (C-6), 28.82 (C-9), 25.81 (C-8), 20.73 [OC(O)*C*H$_3$], 18.98 (2-*C*H$_3$). − MS; *m/z* (%): 241 (53.0) [M^+ + 1], 198 (17.9), 181 (22.7), 43 (100.0). − Peak match: calcd. 240.0998; found 240.09986 ± 0.00092. − $C_{12}H_{16}O_5$ (240.3): calcd. C 59.64, H 6.64; found C 59.99, H 6.71.

7-[(Benzyloxy)methyl]-2-methyl-4,10-dioxatricyclo[5.2.1.0^{2,6}]decan-3-one (**20a**): Oil, yield 49%. − IR (KBr): $\tilde{\nu}$ = 1766 cm^{-1} (C=O). − ^{1}H NMR (400 MHz): δ = 7.33 (m, 5 H, H_{Ph}), 4.60 (d, J_{gem} = 12.05 Hz, 1 H, PhC*H*HOR), 4.56 (d, $J_{1\text{-}9}$ = 4.79 Hz, 1 H, 1-H), 4.52 (d, J_{gem} = 12.03 Hz, 1 H, PhCH*H*OR), 4.26 (dd, J_{gem} = 10.30 Hz, $J_{5\text{-}6}$ = 3.09 Hz, 1 H, 5-H), 4.19 (dd, J_{gem} = 10.15 Hz, $J_{5'\text{-}6}$ = 8.09 Hz, 1 H, 5′-H), 3.87 (d, J_{gem} = 9.85 Hz, 1 H, 7-C*H*HOR), 3.73 (d, J_{gem} = 9.85 Hz, 1 H, 7-CH*H*OR), 2.29 (dd, $J_{6\text{-}5}$ = 3.07 Hz, $J_{6\text{-}5'}$ = 8.11 Hz, 1 H, 6-H), 1.64−1.99 (m, 4 H, 8/9-H), 1.34 (s, 3 H, 2-CH_3). − ^{13}C NMR (25 MHz): δ = 181.19 (C-3), 137.56 (C_{Ph}), 128.48 (C_{Ph}), 127.95 (C_{Ph}), 127.78 (C_{Ph}), 88.17 (C-7), 83.03 (C-1), 73.74 (Ph-*C*H$_2$O), 69.49 (C-5), 66.86 (1-*C*H$_2$O), 53.83 (C-2), 51.32 (C-6), 32.87 (C-8), 25.26 (C-9), 17.54 (2-*C*H$_3$). − MS; *m/z* (%): 288 (6.2) [M^+], 197 (4.8), 181 (10.7), 91 (100.0). − Peak match: calcd. 288.1361; found 288.1361 ± 0.0014.

1-[(Benzyloxy)methyl]-2-methyl-4,10-dioxatricyclo[5.2.1.0^{2,6}]decan-3-one (**20b**): Yield 35%. − M.p. 99°C. − IR (KBr): $\tilde{\nu}$ = 1745 (C=O). − ^{1}H NMR (400 MHz): δ = 7.25−7.34 (m, 5 H, H_{Ph}), 4.65 (d, J_{gem} = 11.98 Hz, 1 H, PhCH*H*OR), 4.57 (d, J_{gem} = 12.00 Hz, 1 H, PhC*H*HOR), 4.40 (d, $J_{7\text{-}8}$ = 5.25 Hz, 1 H, 7-H), 4.38 (pseudo-t, J = 9.2 Hz, 1 H, 5-H), 4.07 (dd, J_{gem} = 9.73 Hz, $J_{5'\text{-}6}$ = 3.85 Hz, 1 H, 5′-H), 3.95 (d, J_{gem} = 11.24 Hz, 1 H, 1-CH*H*OR), 3.89 (d, J_{gem} = 11.25 Hz, 1 H, 1-C*H*HOR), 2.33 (dd, $J_{6\text{-}5}$ = 8.91 Hz, $J_{6\text{-}5'}$ = 3.85 Hz, 1 H, 6-H), 1.88−2.02 (3 × m, 3 H, 8/9-H), 1.53 (m, 1 H, 8/9-H), 1.39 (s, 3 H, 2-CH_3). − ^{13}C NMR (100 MHz): δ = 179.22 (C-3), 138.21 ($C_{Ph,ipso}$), 128.26 (C_{Ph}), 127.60 (C_{Ph}), 127.47 (C_{Ph}), 89.70 (C-1), 82.85 (C-7), 73.57 (Ph*C*H$_2$OR), 70.83 (C-5), 67.97 (1-*C*H$_2$OR), 54.02 (C-2), 51.83 (C-6), 28.83 (C-9), 25.51 (C-8), 19.19 (2-CH$_3$). − MS; *m/z* (%): 289 (9.2) [M^+ + 1], 197 (23.2), 181 (15.8), 91 (100.0). − Peak match: calcd. 288.1361; found 288.1362 ± 0.0011. − $C_{17}H_{20}O_4$ (288.3): calcd. C 70.81, H 6.99; found C 70.64, H 6.93.

7-Bromo-3a-methyl-3-oxoperhydro-4-isobenzofuranyl Acetate (**21**): A mixture of lactone **8** (2.0 g, 12 mmol), acetyl bromide (3.0 g, 24 mmol), and radical inhibitor (5 mg, 0.014 mmol) was diluted up to 15 ml with dichloromethane. The solution was kept at 12 kbar during 16 h, depressurised, and concentrated in vacuo. The residue was purified by column chromatography (hexane/ethyl acetate = 4:1 v/v), affording **21** (3.3 g, 94%) as a white solid, m.p. 79−80°C. − ^{1}H NMR (300 MHz): δ = 4.99 (dd, $J_{4\text{-}5}$ = 2.8 Hz, $J_{4\text{-}5'}$ = 5.0 Hz, 1 H, 4-H), 4.37 (pseudo-t, J = 8.4 Hz, 1 H, 1-H), 4.29 (m, 1 H, 7-H), 4.04 (pseudo-t, J = 8.9 Hz, 1 H, 1′-H), 2.87 (pseudo-dt, $J_{7a\text{-}7}$ = 4.47 Hz, J = 8.5 Hz, 1 H, 7a-H), 1.80−2.28 (m, 4 H, 5/6-H), 2.05 [s, 3 H, 4-OC(O)CH_3], 1.49 (s, 3 H, 3a-CH_3). − $C_{11}H_{15}O_4Br$ (291.1): calcd. C 45.38, H 5.19; found C 45.59, H 5.15.

7-(Acetyloxy)-7a-methyl-1-oxoperhydro-4-isobenzofuranyl 2,2,2-Trifluoroacetate (**22**): A mixture of acetic acid (0.871 g, 14.4 mmol) and trifluoroacetic anhydride (3.21 g, 15.3 mmol) was stirred at room temperature for 0.5 h. To this mixture 1,2-dichloroethane (12 ml), lactone **8** (1.0 g, 5.9 mmol), and radical inhibitor (3 mg, 0.008 mmol) were added. This solution was kept at 15 kbar for 48 h, depressurised, and concentrated in vacuo. The mixture of **22** and **23** was partly purified by bulb-to-bulb distillation (160−180°C/0.8 Torr). Pure **22** was obtained by crystallisation of the crude distillate from hexane/ethyl acetate (7:3 v/v) and recrystallisation from diiso-

propyl ether. Yield 274 mg (14%) of colourless crystals, m.p. 118−120°C. − ^{1}H NMR (400 MHz): δ = 5.25 (br. d, *J* = 2.6 Hz, 1 H, 4-H), 5.05 (br. s, 1 H, 7-H), 4.42 (pseudo-t, *J* = 8.7 Hz, 1 H, 3-H), 4.04 (dd, J_{gem} = 11.45 Hz, $J_{3'\text{-}3a}$ = 8.67 Hz, 1 H, 3′-H), 2.65 (br. t, *J* = 7.53 Hz, 1 H, 3a-H), 2.06 [s, 3 H, 7-OC(O)CH_3], 1.87−2.09 (m, 4 H, 5/6-H), 1.41 (s, 3 H, 7a-H). − $C_{13}H_{15}F_3O_6$ (324.3): calcd. C 48.15, H 4.66; found C 48.44, H 4.61.

3a-Methyl-3-oxo-1,3,3a,4,5,7a-hexahydro-4-isobenzofuranyl Acetate (**23**): A mixture of bromide **21** (0.58 g, 2.0 mmol), potassium acetate (2.0 g, 20 mmol) and tetrabutylammonium acetate (0.2 g, 0. 7 mmol) in acetonitrile/water (6 ml, 5:1 v/v) was stirred for 12 h at 100°C. After cooling the reaction mixture to room temperature, water (10 ml) was added and the resulting solution was extracted twice with dichloromethane. The organic layer was dried with Na_2SO_4, filtered, and concentrated in vacuo. The crude product was distilled, affording **23** (0.35 g, 84%) as a colourless oil. − ^{1}H NMR (300 MHz): 5.72 (m, 2 H, 6-H + 7-H), 5.04 (t, $J_{4\text{-}5}$ = 3.6 Hz, $J_{4\text{-}5'}$ = 3.6 Hz, 1 H, 4-H), 4.44 (pseudo-t, *J* = 8.5 Hz, 1 H, 1-H), 3.99 (pseudo-t, *J* = 8.8 Hz, 1 H, 1′-H), 2.83 (m, 1 H, 7a-H), 2.37 (m, 2 H, 5-H + 5′-H), 2.00 [s, 3 H, 4-OC(O)CH_3], 1.26 (s, 3 H, 3a-CH_3). − Peak match: calcd. 210.0892; found 210.0891 ± 0.0010.

Dimethyl 6-(Acetyloxy)-1,3-dimethyl-3-cyclohexene-1,2-dicarboxylate (**24**) *and Methyl 2-(Acetyloxy)-1,5-dimethyl-7-oxo-6-oxabicyclo[3.2.1]octane-8-carboxylate* (**25**). − *Method 1:* A mixture of trifluoroacetic acid (2.42 g, 21.2 mmol) and acetic anhydride (2.28 g, 22.4 mmol) was stirred at room temperature for 0.5 h. To this mixture dichloromethane (11 ml), dimethyl ester **7** (2.66 g, 11.0 mmol), and radical inhibitor (4 mg, 0.011 mmol) were added. This solution was kept at 15 kbar for 3 h, depressurised, diluted with dichloromethane (10 ml) and washed with a saturated $NaHCO_3$ solution. The organic layer was dried with Na_2SO_4, and concentrated in vacuo. Crude **24** and **25** were separated by column chromatography (hexane/ethyl acetate = 2:1 v/v), affording hexene **24** (2.12 g, 68%) as an oil and lactone **25** (0.250 g, 22%) as a white solid.

Method 2: The same procedure was applied as in Method 1, except that 4 equivalents of acetyl bromide were used instead of the mixture of trifluoroacetic acid and acetic anhydride; yield of lactone **25** 81%.

24: ^{1}H NMR (300 MHz): δ = 5.46 (br. s, 1 H, 4-H), 5.21 (t, $J_{6\text{-}5}$ = 3.8 Hz, $J_{6\text{-}5'}$ = 3.8 Hz, 1 H, 6-H), 3.70 [s, 3 H, C(O)OCH_3], 3.66 [s, 3 H, C(O)OCH_3], 3.14 (s, 1 H, 2-H), 2.30 (br. s, 2 H, 5-H + 5′-H), 1.93 [s, 3 H, 6-OC(O)CH_3], 1.82 (d, *J* = 1.55 Hz, 3 H, 3-CH_3), 1.25 (s, 3 H, 1-CH_3). − ^{13}C NMR (75 MHz): δ = 173.91 [1-*C*(O)OCH$_3$], 171.48 [6-O*C*(O)CH$_3$], 169.70 [2-*C*(O)OCH$_3$], 129.22 (C-3), 119.95 (C-4), 69.69 (C-6), 51.92 [C(O)O*C*H$_3$], 51.78 [C(O)O*C*H$_3$], 51.54 (C-2), 47.20 (C-1), 29.15 (C-5), 23.69 (3-*C*H$_3$), 22.04 [6-OC(O)*C*H$_3$], 20.95 (1-*C*H$_3$). − MS; *m/z* (%): 284 (0.84) [M$^+$], 253 (7.1), 225 (8.3), 211 (38), 43 (100). − Peak match: calcd. 284.1260; found 284.1260 ± 0.005.

25: M.p. 112°C. − ^{1}H NMR (300 MHz): δ = 4.90 (br. t, *J* = 8.4 Hz, 1 H, 2-H), 3.75 [s, 3 H, 8-C(O)OCH_3], 2.71 (s, 1 H, 8-H), 2.18 (m, 1 H, 3/4-H), 2.09 [s, 3 H, 2-OC(O)CH_3], 2.01 (m, 1 H, 3/4-H), 1.69 (m, 2 H, 3/4-H), 1.42 (s, 3 H, 5-CH_3), 1.17 (s, 3 H, 1-CH_3). − ^{13}C NMR (75 MHz): δ = 174.88 (C-7), 170.41 [2-O-*C*(O)CH$_3$], 169.19 [8-*C*(O)OCH$_3$], 81.34 (C-5), 72.86 (C-2), 60.39 (C-8), 52.04 [8-C(O)O*C*H$_3$], 50.64 (C-1), 35.04 (C-4), 25.70 (C-3), 21.67 [2-OC(O)*C*H$_3$], 20.87 (C-1), 13.38 (C-5). − MS; *m/z* (%): 271 (5.7) [M$^+$ + 1], 270 (0.7) [M$^+$], 211 (3.4), 43 (100). − $C_{13}H_{18}O_6$ (270.3): calcd. C 57.77, H 6.71; found C 57.74, H 6.61.

7,7a-Dimethyl-1-oxo-1,3,3a,4,5,7a-hexahydro-4-isobenzofuranyl Acetate (**26**): The same procedure was applied as for **24**/**25**, except that the reaction was carried out at 12 kbar for 7 h. The crude product was recrystallised from consecutively diisopropyl ether and *n*-hexane. Yield 90%, colourless crystals, m.p. 77°C. − IR (KBr): $\tilde{\nu}$ = 1739 cm^{-1}, 1773 (C=O). − ^{1}H NMR (300 MHz): δ = 5.47 (br. s, 1 H, 6-H), 5.22 (ddd, $J_{4\text{-}3a}$ = 4.59 Hz, *J* = 6.43 Hz, *J* = 9.69 Hz, 1 H, 4-H), 4.30 (pseudo-t, *J* = 8.6 Hz, 1 H, 3-H), 4.19 (pseudo-t, *J* = 9.6 Hz, 1 H, 3′-H), 2.82 (ddd, $J_{3a\text{-}4}$ = 4.52 Hz, $J_{3a\text{-}3}$ = 8.03 Hz, $J_{3a\text{-}3'}$ = 10.05 Hz, 1 H, 3a-H), 2.50 (ddt, *J* = 17.7 Hz, *J* = 5.60 Hz, *J* = 1.08 Hz, 1 H, 5-H), 2.18 (m, 1 H, 5′-H), 2.06 [s, 3 H, 4-OC(O)CH_3], 1.77 (d, *J* = 1.32 Hz, 3 H, 7-CH_3), 1.42 (s, 3 H, 7a-CH_3). − ^{13}C NMR (100 MHz): δ = 177.36 (C-1), 170.26 [4-O*C*(O)CH$_3$], 131.48 (C-7), 121.45 (C-6), 67.29 (C-4), 65.60 (C-3), 47.95 (C-7a), 45.25 (C-3a), 26.90 (C-5), 22.00 (7-*C*H$_3$), 21.03 [4-OC(O)*C*H$_3$], 17.38 (7a-*C*H$_3$). − MS; *m/z* (%): 225 (5.1) [M$^+$ + 1], 165 (7.4), 120 (28.9), 105 (100.0). − $C_{12}H_{16}O_4$ (224.3): calcd. C 64.27, H 7.19; found C 64.14, H 7.26.

7-(Hydroxymethyl)-2-methyl-4,10-dioxatricyclo[5.2.1.0^{2,6}]decan-3-one (**27a**). − *Starting with Lactone* **19a**: To a solution of lactone **19a** (0.3 g, 1.25 mmol) in methanol/water (11 ml, 10:1 v/v) Na_2CO_3 (150 mg, 1.4 mmol) was added. The suspension was stirred at room temperature for 1 h. The reaction mixture was then acidified with a 1 N HCl solution and concentrated in vacuo. The residue was dissolved in dichloromethane (10 ml). The solution was washed with a saturated $NaHCO_3$ solution and dried with Na_2SO_4. Evaporation of the solvent afforded alcohol **27a** (0.227 g, 92%) as a white solid.

Starting with Lactone **20a**: A solution of lactone **20a** (2 g, 6.9 mmol) in ethanol/ethyl acetate (55 ml, 10:1 v/v) was stirred under a 40 bar hydrogen atmosphere in the presence of 10% palladium on activated coal as a catalyst for 15 h. The reaction mixture was filtered and the filtrate was concentrated in vacuo, affording alcohol **26a** (1.36 g, 99%) as a white solid, m.p. 135°C. − IR (KBr): $\tilde{\nu}$ = 3458 cm^{-1} (OH), 1746 (C=O). − ^{1}H NMR (400 MHz): δ = 4.57 (d, 1 H, 1-H), 4.56 (dd, $J_{5\text{-}6}$ = 2.48 Hz, 1 H, 5-H), 4.24 (dd, J_{gem} = 10.20 Hz, $J_{5'\text{-}6}$ = 8.15 Hz, 1 H, 5′-H), 4.01 (d, J_{gem} = 11.78 Hz, 1 H, 7-C*H*HOH), 3.95 (d, J_{gem} = 11.76 Hz, 1 H, 7-CH*H*OH), 2.50 (br. s, 1 H, 1-CH$_2$O*H*), 2.28 (dd, $J_{6\text{-}5}$ = 2.54 Hz, $J_{6\text{-}5'}$ = 8.11 Hz, 1 H, 6-H), 1.97 (m, 1 H, 8/9-H), 1.76−1.87 (m, 2 H, 8/9-H), 1.55 (m, 1 H, 8/9-H), 1.36 (s, 3 H, 2-CH_3). − ^{13}C NMR (100 MHz): δ = 181.30 (C-3), 89.12 (C-7), 82.84 (C-1), 66.62 (C-5), 62.14 (1-*C*H$_2$OH), 54.13 (C-2), 51.22 (C-6), 31.30 (C-8), 25.27 (C-9), 17.21 (2-*C*H$_3$). − MS; *m/z* (%): 198 (31.5) [M$^+$], 181 (17.7), 140 (52.7), 39 (100.0). − $C_{10}H_{14}O_4$ (198.2): calcd. C 60.60, H 7.12; found C 60.40, H 7.05.

1-(Hydroxymethyl)-2-methyl-4,10-dioxatricyclo[5.2.1.0^{2,6}]decan-3-one (**27b**). − *Starting with Lactone* **19b**: The same procedure was applied as for alcohol **27a**. Yield 91%.

Starting with Lactone **20b**: The same procedure was applied as for alcohol **27a**. Yield 100%, white solid, m.p. 103°C. − IR (KBr): $\tilde{\nu}$ = 3460 cm^{-1} (OH), 1754 (C=O). − ^{1}H NMR (400 MHz): δ = 4.44 (pseudo-t, *J* = 9.3 Hz, 1 H, 5-H), 4.41 (d, $J_{7\text{-}8}$ = 5.5 Hz, 1 H, 7-H), 4.10 (dd, J_{gem} = 9.46 Hz, $J_{5'\text{-}6}$ = 4.14 Hz, 1 H, 5′-H), 4.02 (br. s, 2 H, 1-C*H*$_2$OH), 2.57 (br. s, 1 H, 1-CH$_2$O*H*), 2.38 (dd, $J_{6\text{-}5}$ = 9.01 Hz, $J_{6\text{-}5'}$ = 4.14 Hz, 1 H, 6-H), 2.11 (m, 1 H, 8/9-H), 1.94 (m, 1 H, 8/9-H), 1.78 (m, 1 H, 8/9-H), 1.61 (m, 1 H, 8/9-H), 1.46 (s, 3 H, 2-CH_3). − ^{13}C NMR (100 MHz): δ = 180.70 (C-3), 90.11 (C-1), 82.45 (C-7), 71.38 (C-5), 62.69 (1-*C*H$_2$OH), 54.15 (C-2), 52.53 (C-6), 29.09 (C-9), 27.07 (C-8), 19.90 (2-*C*H$_3$). − MS; *m/z* (%): 199 (83.6) [M$^+$ + 1], 181 (12.5), 39 (100.0). − Peak match: calcd. 198.0892; found 198.0889 ± 0.0012. − $C_{10}H_{14}O_4$ (198.2): calcd. C 60.60, H 7.12; found C 60.55, H 7.08.

{6-Methyl-5-oxo-4,10-dioxatricyclo[5.2.1.0^{2,6}]dec-1-yl}methyl p-Toluenesulfonate (**28a**): To a solution of alcohol **27a** (0.5 g, 2.52 mmol) in dichloromethane (20 ml), which was cooled to 0°C, tosyl chloride (0.67 g, 3.53 mmol), triethylamine (0.36 g, 3.53 mmol), and 4-(dimethylamino)pyridine (15.4 mg, 0.13 mmol) were added. The solution was stirred at 0°C for 0.5 h and then at room temperature for 2 h. The reaction mixture was washed with water (10 ml) and the organic layer was dried with Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography (ethyl acetate/hexane = 3:2 v/v), affording **28a** (0.693 mg, 78%) as a white solid, m.p. 155−159°C. − IR (KBr): $\tilde{\nu}$ = 1751 cm^{-1} (C=O). − ^{1}H NMR (400 MHz): δ = 7.79 (d, *J* = 8.27 Hz, 2 H, H_{Ph}), 7.38 (d, *J* = 8.15 Hz, 2 H, H_{Ph}), 4.57 (d, $J_{7\text{-}8}$ = 4.98 Hz, 1 H, 7-H), 4.40 (d, J_{gem} = 10.30 Hz, 1 H, 1-C*H*HOR), 4.19 (d, J_{gem} = 10.29 Hz, 1 H, 1-CH*H*OR), 4.19 (dd, J_{gem} = 10.59 Hz, $J_{3\text{-}2}$ = 8.18 Hz, 1 H, 3-H), 4.09 (dd, J_{gem} = 10.61 Hz, $J_{3'\text{-}2}$ = 2.88 Hz, 1 H, 3′-H), 2.47 (s, 3 H, Ph-CH_3), 2.33 (dd, $J_{2\text{-}3}$ = 8.17 Hz, $J_{2\text{-}3'}$ = 2.87 Hz, 1 H, 2-H), 1.97 (m, 1 H, 8/9-H), 1.80 (m, 1 H, 8/9-H), 1.66 (m, 2 H, 8/9-H), 1.34 (s, 3 H, 6-CH_3). − ^{13}C (100 MHz): δ = 180.53 (C-5), 145.67 (C_{Ph}), 132.04 (C_{Ph}), 130.22 (C_{Ph}), 128.09 (C_{Ph}), 88.82 (C-1), 83.61 (C-7), 68.58 (1-*C*H$_2$OR), 66.40 (C-3), 53.97 (C-6), 51.13 (C-2), 32.47 (C-9), 25.26 (C-8), 21.77 (Ph-*C*H$_3$), 17.51 (6-*C*H$_3$). − MS; *m/z* (%): 352 (7.8) [M$^+$], 288 (14.5), 181 (25.3), 91 (100.0). − $C_{17}H_{21}O_6S$ (352.4): calcd. C 57.94 , H 5.72, S 9.10; found C 57.62, H 5.68, S 8.74.

{2-Methyl-3-oxo-4,10-dioxatricyclo[5.2.1.0^{2,6}]dec-1-yl}methyl p-Toluenesulfonate (**28b**): The same procedure was applied as for **28a**, except that the reaction was stirred at room temperature for 5 h. Yield 61%, m.p. 143°C. − IR (KBr): $\tilde{\nu}$ = 1754 cm^{-1} (C=O). − ^{1}H NMR (400 MHz): δ = 7.80 (d, *J* = 8.25 Hz, 2 H, H_{Ph}), 7.35 (d, *J* = 8.13 Hz, 2 H, H_{Ph}), 4.48 (d, J_{gem} = 11.42 Hz, 1 H, 1-CH*H*OR), 4.42 (d, $J_{7\text{-}8}$ = 4.94 Hz, 1 H, 7-H), 4.38 (pseudo-t, *J* = 9.3 Hz, 1 H, 5-H), 4.37 (d, J_{gem} = 11.41 Hz, 1 H, 1-C*H*HOR), 4.06 (dd, J_{gem} = 9.61 Hz, $J_{5'\text{-}6}$ = 3.63 Hz, 1 H, 5′-H), 2.44 (s, 3 H, Ph-CH_3), 2.35 (dd, $J_{6\text{-}5}$ = 8.80 Hz, $J_{6\text{-}5'}$ = 3.64 Hz, 1 H, 6-H), 1.93 (m, 3 H, 8/9-H), 1.58 (m, 1 H, 8/9-H), 1.37 (s, 3 H, 2-CH_3). − ^{13}C NMR (100 MHz): δ = 178.64 (C-3), 144.94 (C_{Ph}), 132.44 (C_{Ph}), 129.88 (C_{Ph}), 127.93 (C_{Ph}), 87.69 (C-1), 83.26 (C-7), 70.90 (C-5), 67.62 (1-*C*H$_2$OR), 54.59 (C-2), 51.46 (C-6), 28.90 (C-9), 25.24 (C-8), 21.61 (*C*H$_3$-Ph), 18.60 (2-*C*H$_3$). − MS; *m/z* (%): 353 (79.9) [M$^+$ + 1], 288 (10.2), 197 (52.1), 181 (100.0). − Peak match: calcd. 352.0981; found 352.0980. − $C_{17}H_{21}O_6S$ (352.4): calcd. C 57.94 , H 5.72, S 9.10; found C 57.76, H 5.578, S 8.77.

7-(Iodomethyl)-2-methyl-4,10-dioxatricyclo[5.2.1.0^{2,6}]decan-3-one (**29a**): A solution of **28a** (1 g, 2.84 mmol) and NaI (1.28 g, 8.53 mmol) in acetonitrile (20 ml) was refluxed for 15 h. The reaction mixture was cooled to room temperature and then filtered. The filtrate was concentrated in vacuo and the residue was purified by column chromatography (hexane/ethyl acetate = 3:2 v/v), affording iodide **29a** (0.842 g, 96%) as a white solid, m.p. 112−118°C. − IR (KBr): $\tilde{\nu}$ = 1757 cm^{-1} (C=O). − ^{1}H NMR (400 MHz): δ = 4.79 (d, $J_{1\text{-}9}$ = 4.74 Hz, 1 H, 1-H), 4.33 (dd, J_{gem} = 10.45, $J_{5\text{-}6}$ = 8.28 Hz, 1 H, 5-H), 4.16 (dd, J_{gem} = 10.50 Hz, $J_{5'\text{-}6}$ = 2.76 Hz, 1 H, H-5′), 3.43 (s, 2 H, 7-CH_2I), 2.48 (dd, $J_{6\text{-}5}$ = 8.23 Hz, $J_{6\text{-}5'}$ = 2.74 Hz, 1 H, 6-H), 1.84−2.01 (m, 3 H, 8/9-H), 1.68 (m, 1 H, 8/9-H), 1.37 (s, 3 H, 2-CH_3). − ^{13}C NMR (100 MHz): δ = 180.60 (C-3), 88.54 (C-7), 84.61 (C-1), 66.48 (C-5), 54.40 (C-2), 52.02 (C-6), 34.69 (C-8), 25.53 (C-9), 17.43 (2-*C*H$_3$), 2.99 (7-*C*H$_2$I). − Peak match: calcd. 307.9911, found 307.9912 ± 0.0011. − MS; *m/z* (%): 308 (12.7) [M$^+$], 181 (100.0), 83 (48.5). − $C_{10}H_{13}IO_3$ (308.1): calcd. C 38.98, H 4.25; found C 39.14, H 4.33.

1-(Iodomethyl)-2-methyl-4,10-dioxatricyclo[5.2.1.0^{2,6}]decan-3-one (**29b**): The same procedure was applied as for iodide **29a**, except that 10 equivalents of NaI were used and that the reaction time was prolonged to 5 d. Yield 89%, m.p. 129°C. − IR (KBr): $\tilde{\nu}$ = 1738 cm^{-1} (C=O). − ^{1}H NMR (400 MHz): δ = 4.42 (d, $J_{7\text{-}8}$ = 3.50 Hz, 1 H, 7-H), 4.41 (pseudo-t, *J* = 9.2 Hz, 1 H, 5-H), 4.10 (dd, J_{gem} = 9.49 Hz, $J_{5'\text{-}6}$ = 3.79 Hz, 1 H, 5′-H), 3.88 (d, J_{gem} = 11.48 Hz, 1 H, 1-CH*H*I), 3.57 (d, J_{gem} = 11.48 Hz, 1-C*H*HI), 2.49 (dd, $J_{6\text{-}5}$ = 8.86 Hz, $J_{6\text{-}5'}$ = 3.78 Hz, 1 H, 6-H), 1.95−2.03 (m, 3 H, 8/9-H), 1.64 (m, 1 H, 8/9-H), 1.45 (s, 3 H, 2-CH_3). − ^{13}C NMR (100 MHz): δ = 179.21 (C-3), 88.15 (C-1), 82.65 (C-7), 70.97 (C-5), 54.02 (C-2), 53.17 (C-6), 30.59 (C-9), 29.83 (C-8), 19.35 (2-*C*H$_3$), 4.43 (1-*C*H$_2$I). − MS; *m/z* (%): 309 (4.1) [M$^+$ + 1], 210 (18.1), 181 (35.1), 83 (100.0). − Peak match: calcd. 307.9911; found 307.9911 ± 0.0009. − $C_{10}H_{13}IO_3$ (308.1): calcd. C 38.98, H 4.25; C 39.17, H 4.33.

7-Hydroxy-7a-methyl-4-methyleneperhydro-1-isobenzofuranone (**30a**): To a solution of iodide **29a** (500 mg, 1.62 mmol) in ethanol (20 ml) zinc (130 mg, 1.99 mmol) was added. The reaction mixture was then refluxed for 1 h, cooled to room temperature, filtered, and concentrated in vacuo. The crude product was purified by column chromatography (hexane/ethyl acetate = 2:1 v/v), affording **30a** (264 mg, 89%) as a white solid, m.p. 140−141°C. − IR (KBr): $\tilde{\nu}$ = 3386 cm^{-1} (OH), 1742 (C=O). − ^{1}H NMR (400 MHz): δ = 4.96 (s, 1 H, =CH*H*), 4.89 (s, 1 H, =C*H*H), 4.30 (dd, J_{gem} = 11.03 Hz, $J_{3\text{-}3a}$ = 8.31 Hz, 1 H, 3-H), 4.18 (pseudo-t, *J* = 8.6 Hz, 1 H, 3′-H), 3.93 (br. s, 1 H, 7-H), 2.93 (pseudo-t, *J* = 9.9 Hz, H_{3a}), 2.82 (d, *J* = 4.78 Hz, 1 H, 7-O*H*), 2.65 (tt, *J* = 13.83 Hz, *J* = 2.03 Hz, 1 H, 5-H), 2.12 (m, 1 H, 5′-H), 1.89 (m, 1 H, 6-H), 1.72 (m, 1 H, 6′-H), 1.20 (s, 3 H, 7a-CH_3). − ^{13}C NMR (100 MHz): δ = 181.27 (C-1), 141.55 (C-4), 113.68 (=*C*H$_2$), 70.40 (C-7), 69.38 (C-3), 49.52 (C-3a), 48.91 (C-7a), 29.73 (C-5), 24.36 (C-6), 20.48 (7a-*C*H$_3$). − MS; *m/z* (%): 183 (74.2) [M$^+$ + 1], 182 (14.8) [M$^+$], 165 (21.1), 154 (11.9), 139 (14.8), 39 (100.0). − $C_{10}H_{14}O_3$ (182.2): calcd. C 65.92, H 7.74; found C 66.02, H 7.65.

4-Hydroxy-7a-methyl-7-methyleneperhydro-1-isobenzofuranone (**30b**): The same procedure was applied as for **30a**, except that the reaction time was prolonged to 2 d. Yield 85%, oil. − IR (KBr): $\tilde{\nu}$ = 3437 cm^{-1} (OH), 1751 (C=O). − ^{1}H NMR (400 MHz): δ = 4.92 (s, 1 H, =C*H*H), 4.88 (s, 1 H, =CH*H*), 4.23 (dd, $J_{3\text{-}3a}$ = 7.73 Hz, J_{gem} = 9.04 Hz, 1 H, 3-H), 4.13 (pseudo-dt, $J_{4\text{-}5'}$ = 11.6 Hz, *J* = 5.4 Hz, 1 H, 4-H), 4.05 (dd, $J_{3'\text{-}3a}$ = 11.27 Hz, J_{gem} = 9.28 Hz, 1 H, 3′-H), 2.65 (pseudo-dt, $J_{3a\text{-}3'}$ = 11 Hz, *J* = 6 Hz, 1 H, 3a-H), 2.20 (br. s, 1 H, 4-O*H*), 2.27 (m, 2 H, 6-H), 1.88 (m, 1 H, 5-H), 1.59 (m, 1 H, 5′-H), 1.32 (s, 7a-CH_3). − ^{13}C NMR (100 MHz): δ = 178.97 (C-1), 142.78 (C-7), 112.68 (=*C*H$_2$), 66.85 (C-4), 65.96 (C-3), 49.02 (C-3a), 49.02 (C-7a), 31.11 (C-6), 29.94 (C-5), 21.77 (7a-*C*H$_3$). − MS; *m/z* (%): 183 (6.2) [M$^+$ + 1], 123 (100.0). − Peak match: calcd. 182.0943; found 182.09430 ± 0.00090.

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