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A concise methodology for the synthesis of (−)-Δ⁹-tetrahydrocannabinol and (−)-Δ⁹-tetrahydrocannabivarin metabolites and their regiospecifically deuterated analogs

Spyros P. Nikas,[a,*] Ganesh A. Thakur,[a] Damon Parrish,[b] Shakiru O. Alapafuja,[a] Marilyn A. Huestis[c] and Alexandros Makriyannis[a,*]

[a]*Center for Drug Discovery, Northeastern University, 116 Mugar Life Sciences Building, 360 Huntington Avenue, Boston, MA 02115, USA*
[b]*Naval Research Laboratory, Code 6030, 4555 Overlook Avenue, Washington, DC 20375, USA*
[c]*Chemistry and Drug Metabolism Section, CPTR Branch, Intramural Research Program, NIDA, NIH, 5550 Nathan Shock Drive, Baltimore, MD 21224, USA*

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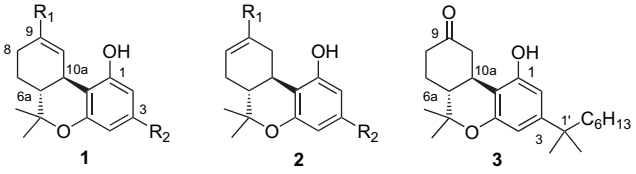
Abstract—The availability of tetrahydrocannabinols (Δ⁹-THC), tetrahydrocannabivarins (Δ⁹-THCV), and their metabolites in both their undeuterated and deuterated forms is critical for the analysis of biological and toxicological samples. We report here a concise methodology for the syntheses of (−)-Δ⁹-THC and (−)-Δ⁹-THCV metabolites in significantly improved overall yields using commercially available starting materials. Our approach allowed us to obtain the key intermediates (6a*R*,10a*R*)-9-nor-9-oxo-hexahydrocannabinols in four steps from (+)-(1*R*)-nopinone. This was followed by an optimized Shapiro reaction to give the (−)-11-nor-9-carboxy-metabolites, which were converted to their respective (−)-11-hydroxy analogs. The synthetic sequence involves a minimum number of steps, avoids undesirable oxidative conditions, and incorporates the costly deuterated resorcinols near the end of the synthetic sequence. This methodology enabled us to synthesize eight regiospecifically deuterated (−)-Δ⁹-THC and (−)-Δ⁹-THCV metabolites in a preparative scale and high optical purity without deuterium scrambling or loss.

1. Introduction

The availability of tetrahydrocannabinols and their metabolites in both their undeuterated and deuterated forms is critical for the analysis of biological and toxicological samples.[1–22] A recent study tracing the metabolism of marijuana constituents including (−)-(6a*R*,10a*R*)-Δ⁹-tetrahydrocannabinol [(−)-Δ⁹-THC, **1a**] and (−)-(6a*R*,10a*R*)-Δ⁹-tetrahydrocannabivarin [(−)-Δ⁹-THCV,[23] **1b**] (Fig. 1) in humans required the synthesis of deuterated tetrahydrocannabinols **1c** and **1d** and tetrahydrocannabivarins **1e** and **1f** as well as their corresponding in vivo metabolites **18b**–**18e** and **21b**–**21e** (Scheme 1) in high isotopic and optical purities. We have already reported the efficient syntheses of the labeled (−)-Δ⁹-derivatives **1c**–**1f** without deuterium scrambling or loss.[24–26] We now report the successful synthesis of regiospecifically deuterated 11-nor-9-carboxy and 11-hydroxy metabolites of (−)-Δ⁹-THC (**18b**, **18c**, **21b**, **21c**) and (−)-Δ⁹-THCV (**18d**, **18e**, **21d**, **21e**) in preparative scales.

Although a number of approaches have been reported[1–4,11–22,27–31] for the synthesis of tetrahydrocannabinol metabolites and closely related analogs, only a small number of



a: $R_1 = CH_3$, $R_2 = (CH_2)_4CH_3$
b: $R_1 = CH_3$, $R_2 = (CH_2)_2CH_3$
c: $R_1 = CH_3$, $R_2 = (CH_2)_3C^2H_2C^2H_3$
d: $R_1 = CH_3$, $R_2 = (CH_2)_4C^2H_3$
e: $R_1 = CH_3$, $R_2 = CH_2C^2H_2C^2H_3$
f: $R_1 = CH_3$, $R_2 = (CH_2)_2C^2H_3$

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g: $R_1 = CH_2OH$, $R_2 = (CH_2)_4CH_3$
h: $R_1 = COOH$, $R_2 = (CH_2)_4CH_3$
i: $R_1 = CH_2OCOCH_3$, $R_2 = (CH_2)_4CH_3$
j: $R_1 =$  , $R_2 = (CH_2)_4CH_3$

Figure 1.

Keywords: (−)-Δ⁹-Tetrahydrocannabinol; (−)-Δ⁹-Tetrahydrocannabivarin; Metabolites; Shapiro reaction; Regiospecifically deuterated analogs.
* Corresponding authors. Tel.: +1 617 373 4200; fax: +1 617 373 7493; e-mail addresses: s.nikas@neu.edu; a.makriyannis@neu.edu

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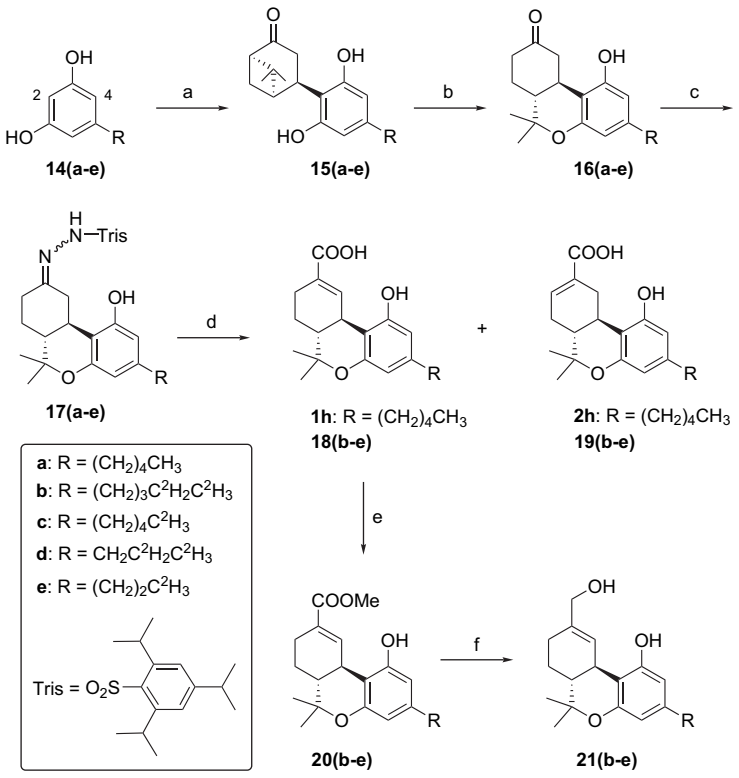

Scheme 1. Reagents and conditions: (a) **8**, *p*-TSA-H_2O, $CHCl_3$, 0 °C to room temperature, 3.5 days, 31–33%; (b) TMSOTf, CH_2Cl_2/CH_3NO_2 (3:1), 0 °C, 6 h, 69–72%; (c) 2,4,6-triisopropylbenzenesulfonylhydrazide, benzene, 40–42 °C, 10 min; (d) (i) *n*-BuLi (portionwise addition), hexane/TMEDA (1:1), −78 °C to 0 °C, 1.5 h, then CO_2, 0 °C, 10 min, 49–51% from **16a** to **16e**; (ii) recrystallization from $CHCl_3$ or $CHCl_3$/hexane gave pure **1h, 18b–18e** in 21–23% from **16a** to **16e**; (e) CH_2N_2, Et_2O, 0 °C, 30 min, quantitative; (f) DIBAL-H, CH_2Cl_2, −78°C, 20 min, 97–98%.

those can provide (−)-Δ^9-THC metabolites in their native 6a*R*,10a*R* absolute configuration in satisfactory quantities. This is due to: (a) the formation of mixtures of C2 and C4 regioisomers during the condensation of the respective resorcinols (**14**) with an appropriate chiral monoterpene; (b) the formation of mixtures of 6a,10a cis and trans isomers during the dibenzo[*b*,*d*]pyran ring closure; (c) the instability of the double bond at C9, which readily isomerizes to the thermodynamically more stable Δ^8-position (**2**, Fig. 1); and (d) the sensitivity of the tetrahydrocannabinol tricyclic ring system to oxidative conditions, particularly in basic media. The determined efforts of two generations of chemists have not totally addressed these problems. An additional consideration for developing improved synthetic approaches was the need to incorporate costly deuterated fragments in the later steps of these syntheses. A summary of existing methodologies is provided below.

An earlier methodology[2] developed for the synthesis of metabolites **1g** and **1h** utilizes (−)-Δ^9-THC (**1a**), which can be obtained from the condensation of olivetol (**14a**) and (+)-*cis*/*trans*-*p*-mentha-2,8-dien-1-ol (**4**) (Fig. 2).[26,32] (−)-Δ^9-THC (**1a**) was converted to (−)-11-hydroxy-Δ^9-THC (**1g**) in seven steps[2] followed by oxidation to (−)-11-nor-9-carboxy-Δ^9-THC (**1h**) in four steps.[2,18,19,31] Later approaches[11,18,31] involved the condensation of olivetol (**14a**) with chiral terpenic synthons **5**[11] or **6**[18,31] where the respective 11 acetoxy derivative **1i** and the masked aldehyde **1j** were intermediates.[11,18–20,31] Also, condensations employing the isopropenyl terpene **7** were low yielding reactions.[18,31] In practice, the total synthesis of tricyclic cannabinoids and related metabolites using either **5**, **6**, or **7** as synthons is laborious because of the multistep procedures required to produce these chiral terpenoids from commercially available starting materials.[11,18,31,33] More recently, following a different approach, ketone **16a** was elaborated using a Shapiro reaction to produce the acid **1h** in 31–54% yield.[29] Synthesis of racemic **16a** can be accomplished in five steps starting with the von Pechmann condensation of olivetol (**14a**) and commercially available diethyl α-acetoglutarate.[34] However, the resolution of racemic **16a** through its (+)-diisopropyl-L-tartrate ketals gives the desired enantiomer (−)-**16a** in only 10% yield.[29]

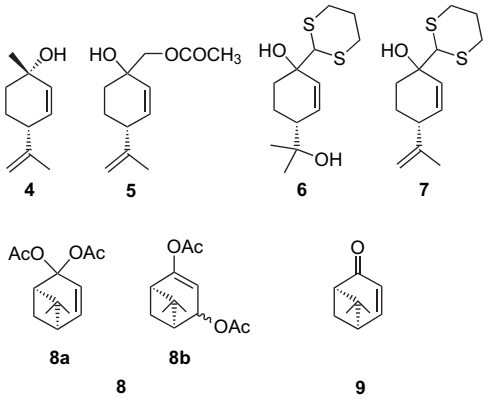

Figure 2.

We now report a significantly more concise methodology using the chiral terpenic synthon **8**[35] for the synthesis of undeuterated and deuterium labeled (−)-Δ^9-THC and (−)-Δ^9-THCV metabolites. The current approach involves fewer than half of the steps involved in the earlier procedures, completely avoids oxidative reaction conditions, and affords over fivefold improvement in overall yield for the final pure products. This method can also be used to obtain regiospecifically deuterated metabolites with no deuterium scrambling or loss.

2. Results and discussion

Reported approaches to acid **1h** via the key intermediate **16a** suffer from extremely low yields and involve multistep procedures necessitating the incorporation of olivetol (**14a**) in early steps of the synthesis.[29,34] While seeking to improve this methodology we have developed a more efficient synthesis of 9-oxo intermediate **16a** from the chiral synthon **8**. This was followed by an optimized Shapiro conversion of **16a**[29] to give the acid metabolites **1h** and **18**, which were subsequently reduced to the corresponding hydroxymethyl metabolites **21**.

Both terpene acetates **8a** and **8b** have been previously utilized individually in the stereospecific syntheses of 9-oxocannabinoids with the required 6a*R*,10a*R* configuration, including the cannabinergic drug nabilone[35] (**3**) and a number of related analogs bearing C1′ substituents.[36,37] However, in our hands and as reported by Tius[36] the use of an **8a** and **8b** mixture led to equally good results thereby minimizing the problem of (+)-apoverbenone (**9**) byproduct formation,[38] which is associated with the synthesis and purification of individual isomers. Thus, transesterification of (+)-(1*R*)-nopinone[35,39–41] with isopropenyl acetate gave (−)-nopinone enol acetate,[35,39] which was then treated with lead tetraacetate in refluxing benzene. The reaction mixture obtained after removal of the insoluble materials was then treated with water and the brown-black precipitate of lead oxide removed. This modification enhanced the yields of the following reaction step, most likely due to the careful removal of lead tetraacetate, which otherwise induces oxidation of resorcinol intermediates.[42,43] Also, the resulting crude mixture **8** of diacetates **8a** and **8b** prepared by this method has excellent long term stability,[44] and was used as such in the subsequent condensation reaction.

Reaction of equimolar amounts of **8** and olivetol (**14a**) in the presence of *p*-toluenesulfonic acid monohydrate at a range of temperatures (−55 °C to 27 °C) and reaction times (2–9 h) using either chloroform or benzene as solvent produced the C2 addition product **15a**[14] in only up to 22% yields. Other major byproducts of this reaction as identified through their isolation and characterization (see Section 4.3) included (+)-apoverbenone (**9**), 2,4-diterpene adduct **10**, byproduct **12**, as well as unreacted olivetol (**14a**). The olivetol that is monosubstituted at C4 with the terpene fragment, a possible product, which was expected to be unstable[32,45] was not isolated from this reaction. We demonstrated that in the absence of olivetol the mixture of diacetates (**8**) is completely converted to (+)-apoverbenone (**9**) in about 1.5 h in the presence of *p*-toluenesulfonic acid. This byproduct formation is one of the reasons for the observed low yield of this reaction. We also showed that **12**, initially identified as a reaction byproduct could be quantitatively converted to the desired keto analog **15a** when stirred at room temperature for 3.5 days, where the deacetylated compound **13** is an intermediate (see Section 4.4). Arguably, both **15a** and **12** are obtained through the common enol acetate intermediate **11** (Chart 1). On the basis of the above findings we were able to improve the yield of this reaction by using an excess of the mixture of diacetates (**8**) and increasing the reaction time.

Our optimized reaction conditions gave **15a** in 33% isolated yield, which upon treatment with catalytic trimethylsilyl triflate in dichloromethane/nitromethane gave **16a** with the required 6a*R*,10a*R* stereochemistry in 72% yield. Treatment of ketone **16a** with trisylhydrazide in benzene at 40–42 °C afforded **17a** as a 2.7:1 mixture of two isomeric trisylhydrazones (**17a$_1$** and **17a$_2$**) by ^{1}H NMR. Since, the geometry[46,47] of the hydrazone may affect the regioselectivity (Δ^8 vs Δ^9) of the subsequent Shapiro reaction, we explored conditions aimed at optimizing the ratio of the isomeric trisylhydrazones[48] however, without any success. Furthermore, separation of **17a$_1$** and **17a$_2$** by flash column chromatography proved to be very laborious and resulted in significant decomposition of both isomers. For this

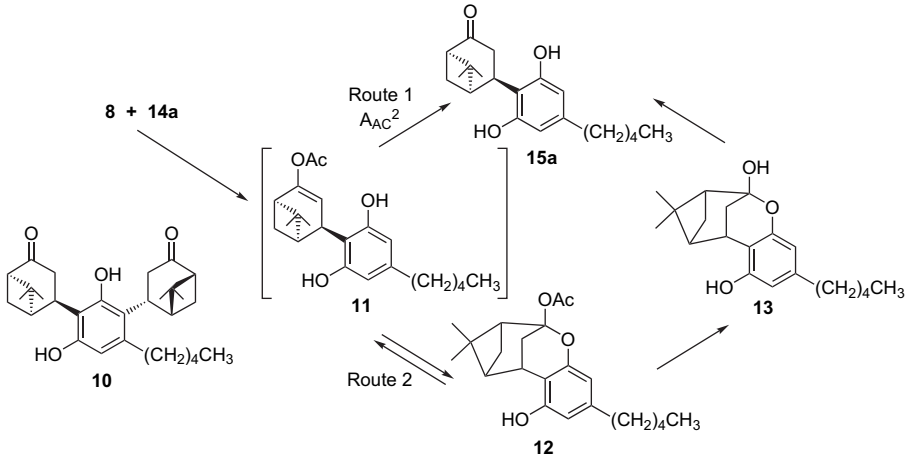

Chart 1.

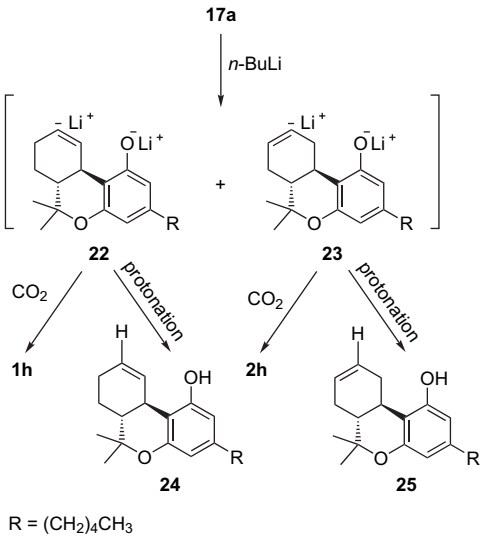

Chart 2.

reason, the mixture **17a** was used as such in the subsequent reactions.[29]

Contrary to an earlier report,[29] the addition of *n*-butyllithium to a solution of **17a** in a mixture of hexane/*N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) (9:1) at −78 °C followed by warming to 0 °C and subsequent treatment with CO_2 produced the Δ^9-isomer **1h** and the Δ^8-isomer **2h** in an almost equimolar ratio. We excluded the possibility of isomerization of **1h** to the thermodynamically more stable **2h** during chromatographic purification[29] of the crude product mixture by showing that no Δ^8-isomer **2h** was detected by ^{1}H NMR after stirring a pure sample of Δ^9-isomer **1h** in ethyl acetate/hexane with silica gel at room temperature for 13 h. The two by-products from this Shapiro reaction, **24** and **25** (Chart 2), were formed in approximately 17% yield, and in the same ratio as the respective Δ^9-acid **1h** to the Δ^8-acid **2h**. These results, thus, support the formation of the isomeric vinyllithium derivatives **22** and **23** as reaction intermediates leading either to the carboxylic acid products (**1h** and **2h**), or to their respective non-carboxylated compounds (**24** and **25**). We obtained similar results when we replaced CO_2 with MeI in the electrophile trapping step and obtained the respective tetrahydrocannabinol analogs.[49] The use of MeLi did not improve the isomer ratio, while other bases (LDA, LiHMDS) did not induce Shapiro decomposition.

It thus appears that the ratio of the Δ^9-isomers to Δ^8-isomers is not dependent on the ratio of the corresponding trisylhydrazones $\mathbf{17a_1}$ and $\mathbf{17a_2}$ suggesting that both hydrazones are capable of forming the Δ^9-isomer as the preferred product. We postulate that the kinetic preference of Δ^9-over the Δ^8-isomer may be due to intramolecular assistance from the phenolate, which favors deprotonation at C10 over C8. We next focused our attention for developing conditions that would allow us to obtain reproducible yields of Δ^9-acid **1h** in larger scale (1–2 g) with the minimum formation of the Δ^8-isomer **2h**. We found that portionwise addition of *n*-BuLi along with increased amounts of TMEDA in the solvent mixture consistently produced a mixture of **1h/2h** in a ratio of 89:11 in 49–50% yields. Recrystallization of this mixture from chloroform afforded the Δ^9-isomer **1h** (99% pure). The concise methodology described above was used as a basis for the synthesis of a series of side chain regiospecifically deuterated analogs. Acid catalyzed coupling of resorcinols **14b–14e**[25,26] with diacetate mixture **8** gave norpinanones **15b–15e**, which are reported for the first time in labeled forms, as white solids in 31–33% yields.

Recrystallization of **15c** from dichloromethane/hexane afforded crystals suitable for X-ray analysis (Fig. 3), thus providing direct evidence on the stereospecificity of this coupling reaction. The crystal structure of **15c** reveals that the cyclohexanone ring in the bicyclic ring system exists in a chair form that is conformationally constrained by the dimethyl substituted cyclobutane ring. In this conformation the phenolic ring assumes an equatorial orientation with its plane nearly at a right angle with the six-membered ring. The crystal structure also reveals the proximity of one of the phenolic groups to the keto group, a conformational feature, which may explain the formation of intermediate **12**. Dibenzo[*b*,*d*]pyran ring closure proceeded smoothly with catalytic trimethylsilyl triflate to give the ketones **16b–16e** in 69–72% yields. The sequence of trisylhydrazone

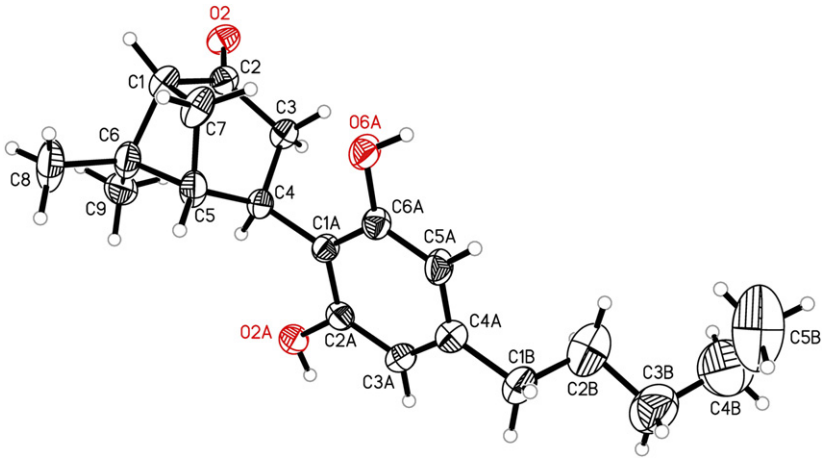

Figure 3. ORTEP structure of **15c**.

formation followed by Shapiro decomposition–electrophile trapping provided mixtures Δ^9-acids **18b–18e** to Δ^8-acids **19b–19e** (87:13) in 49–51% yields. This was followed by recrystallization from chloroform or chloroform/hexane to give the pure Δ^9-isomers **18b–18e** in 21–23% yields from **16b–16e**, respectively. Isotope ratio analysis of the molecular ion cluster using field ionization[25,26] in conjunction with ^{1}H NMR spectral data showed that the percentage of deuterium incorporation in the acids **18b–18e** was identical to that of the starting resorcinols **14b–14e**,[25,26] and clearly indicates that this sequence of reactions did not result in any deuterium loss or scrambling.

In a previous report[22] a racemic 11-nor-9-carboxy-Δ^9-THC was converted to the respective 11-hydroxy-Δ^9-THC in 57% yield by the action of lithium aluminum hydride in THF. We have significantly improved the reductive transformation of the (6a*R*,10a*R*)-Δ^9-acids **18b–18e** to the respective (6a*R*,10a*R*)-Δ^9-alcohols **21b–21e** through a two-step procedure. Titration of **18b–18e** with an ethereal solution of diazomethane[50] at 0 °C afforded the corresponding esters **20b–20e** in quantitative yields. Subsequent reduction of these intermediates with DIBAL-H at −78 °C gave the deuterated (−)-Δ^9-THC and (−)-Δ^9-THCV metabolites **21b–21e** in 97–98% yields. Isotope ratio analysis using field ionization in conjunction with ^{1}H NMR spectral data showed that the percentage of deuterium incorporation in the alcohols **21b–21e** was identical to that of the acids **18b–18e**.

3. Conclusions

We have developed a concise methodology for the synthesis of (−)-Δ^9-THC and (−)-Δ^9-THCV metabolites in significantly improved overall yields. Our synthetic approach: (a) requires fewer than half of the steps involved in the earlier reports; (b) avoids lengthy procedures for the synthesis of the terpene fragment; (c) eliminates the use of oxidative steps that lead to undesirable side products; (d) affords over fivefold improvement in overall yield; and (e) incorporates the costly deuterated resorcinols near the end of the synthetic sequence. Our approach uses an optimized Shapiro reaction as its key step. By employing (+)-(1*R*)-nopinone as the starting material, we obtained in only six steps the desired carboxylic acid (−)-**1h** in preparative scale and high optical purity. Subsequently, the two-step conversion of deuterated (−)-11-nor-9-carboxy-Δ^9-THCs and THCVs gave the respective (−)-11-hydroxy analogs in near quantitative yields. This methodology enabled us to synthesize all eight regiospecifically deuterated (−)-Δ^9-THC and (−)-Δ^9-THCV metabolites (**18b–18e** and **21b–21e**) without deuterium scrambling or loss.

4. Experimental

4.1. Materials

All reagents and solvents were purchased from Aldrich Chemical Company unless otherwise specified and used without further purification. All anhydrous reactions were performed under a static argon or nitrogen atmosphere in flame-dried glassware using scrupulously dry solvents. Flash column chromatography employed silica gel 60 (230–400 mesh). All compounds were demonstrated to be homogeneous by analytical TLC on pre-coated silica gel TLC plates (Merck, 60 F_{245} on glass, layer thickness 250 μm) and chromatograms were visualized by phosphomolybdic acid staining. Melting points were determined on a micro-melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker DMX-500 or on a Varian INOVA-500 spectrometer operating at 500 MHz. All NMR spectra were recorded in $CDCl_3$ unless otherwise stated. Chemical shifts are reported in units of δ relative to internal TMS; multiplicities are indicated as br (broadened), s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and coupling constants (J) are reported in hertz (Hz). Low, high-resolution mass spectra and isotopic ratio analysis were performed at the School of Chemical Sciences, University of Illinois at Urbana-Champaign. Mass spectral data are reported in the form of m/z (intensity relative to base=100).

4.2. Mixture (8) of (+)-6,6-dimethyl-2,2-diacetoxy-3-norpinene[35] (8a) and (−)-6,6-dimethyl-2,4-diacetoxy-2-norpinene[35] (8b)

To a solution of nopinone enol acetate (30 g, 167 mmol) in anhydrous benzene (550 mL) at room temperature under an argon atmosphere was added lead(IV) acetate (111 g, 251 mmol) previously dried in vacuo over P_2O_5/KOH. The reaction mixture was heated at 78–80 °C for 3.5 h with stirring, then cooled to room temperature, and filtered through a short pad of Celite. The filtrate was diluted with diethyl ether and water was added (formation of brown-black lead oxide). The mixture was stirred vigorously for 10 min, then filtered through a short pad of Celite, and the organic phase was separated. The aqueous layer was extracted with diethyl ether, the combined organic layer was washed with brine, dried ($MgSO_4$), and the solvent was evaporated under reduced pressure to give **8** (41 g) as a clear liquid. On the basis of ^{1}H NMR analysis, this crude product contains approximately 87% diacetates **8a** and **8b** (ca. 90% yield) in a ratio 1.63:1, respectively, along with small amounts of (+)-apoverbenone[35,40] [8%, δ: 7.53 (dd, J=9.0, 6.5 Hz, 1H), 5.96 (br d, J=9.0 Hz, 1H)] and traces of unidentified impurities. Compound **8a**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.55 (dd, J=9.0, 6.7 Hz, 1H), 6.29 (dd, J=9.0, 1.9 Hz, 1H), 3.15 (td, J=6.0, 2.2 Hz, 1H), 2.29–2.21 (m, 3H), 2.04 (s, 6H), 1.40 (s, 3H), 1.01 (s, 3H). Compound **8b**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.44 (m as t, J=2.7 Hz, 1H), 5.35 (m, 1H), 2.55–2.49 (m, 2H), 2.47–2.42 (m, 2H), 2.12 (s, 3H), 2.03 (s, 3H), 1.38 (s, 3H), 1.03 (s, 3H).

4.3. (4*R*)-4-(4-Pentyl-2,6-dihydroxyphenyl)-6,6-dimethyl-2-norpinanone (15a)

To a degassed solution of **14a** (2.635 g, 14.64 mmol) and diacetates **8** (5.608 g, ca. 87% pure by ^{1}H NMR, 20.50 mmol) in $CHCl_3$ (147 mL) at 0 °C, under an argon atmosphere was added *p*-toluenesulfonic acid monohydrate (3.895 g, 20.50 mmol). The reaction mixture was warmed to room temperature and stirred for 3.5 days to ensure complete formation of the product. The mixture was diluted with diethyl ether and washed sequentially with water, saturated aqueous $NaHCO_3$, and brine. The organic phase was dried over $MgSO_4$ and the solvent was removed under reduced

pressure. The residue obtained was chromatographed on silica gel (45% diethyl ether in hexane) and fractions containing almost pure product (TLC) were combined and evaporated. Further purification by flash column chromatography on silica gel (27% acetone in hexane) gave **15a**[14] as a white crystalline solid (1.527 g, 33% yield). R_f=0.30 (50% diethyl ether in hexane), R_f=0.33 (30% acetone in hexane). Mp=141–143 °C (from CH_2Cl_2/hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.16 (s, 2H, ArH), 4.79 (br s, 2H, OH), 3.95 (t, J=8.2 Hz, 1H), 3.48 (dd, J=18.8, 7.7 Hz, 1H), 2.62 (dd, J=18.7, 8.5 Hz, 1H), 2.58 (t, J=5.0 Hz, 1H), 2.51 (m, 1H), 2.45 (d, J=10.5 Hz, 1H), 2.43 (t, J=7.7 Hz, 2H, 1′-H), 2.29 (t, J=5.3 Hz, 1H), 1.54 (qt, J=7.7 Hz, 2H, 2′-H), 1.36 (s, 3H, 6-Me), 1.34–1.26 (m, 4H, 3′-H, 4′-H), 1.00 (s, 3H, 6-Me), 0.89 (t, J=7.2 Hz, 3H, 5′-H). Mass spectrum m/z (relative intensity) 316 (M^+, 87), 301 (24), 273 (54), 247 (19), 233 (91), 206 (34), 193 (60), 150 (37), 83 (100). Exact mass calculated for $C_{20}H_{28}O_3$, 316.2038; found, 316.2035.

When the above procedure was carried out using **14a** (1.080 g, 6.0 mmol), **8** (1.641 g, ca. 87% pure by ^{1}H NMR, 6.0 mmol), and *p*-toluenesulfonic acid monohydrate (1.140 g, 6.0 mmol) in $CHCl_3$ (60 mL), and the reaction time was 7.5 h, five major compounds were isolated by flash column chromatography on silica gel (40% diethyl ether in hexane to 80% diethyl ether in hexane): (+)-apoverbenone[35,40] (**9**, 363 mg), **15a** (426 mg, 22%), byproduct **12** (280 mg, 13%), olivetol (**14a**, 265 mg), and diadduct **10** (667 mg, 25%). Compound **12**: pale yellow viscous oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.47 (d, J=2.3 Hz, 1H, ArH), 6.39 (d, J=2.3 Hz, 1H, ArH), 6.16 (s, 1H, OH), 3.69–3.61 (m, 2H), 2.65 (d, J=10.7 Hz, 1H), 2.59–2.53 (m, 3H), 2.51–2.39 (m, 2H), 2.27 (s, 3H, $OCOCH_3$), 2.16 (t, J=5.4 Hz, 1H), 1.55–1.47 (m, 2H, 2′-H), 1.37 (s, 3H, $>C(CH_3)_2$), 1.36–1.27 (m, 4H, 3′-H, 4′-H), 0.99 (s, 3H, $>C(CH_3)_2$), 0.89 (t, J=7.3 Hz, 3H, 5′-H). Mass spectrum m/z (relative intensity) 358 (M^+, 95), 343 (12), 316 (46), 304 (27), 273 (63), 260 (17), 247 (41), 233 (64), 219 (53), 205 (72), 193 (44), 149 (41), 83 (100). Exact mass calculated for $C_{22}H_{30}O_4$, 358.2144; found, 358.2139. Compound **10**: white solid. Mp=107–109 °C (dec); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.21 (s, 1H, ArH), 5.48 (br s, 1H, OH), 5.14 (br s, 1H, OH), 3.73 (t, J=8.0 Hz, 1H), 3.67 (t, J=8.5 Hz, 1H), 3.46 (dd, J=18.8, 7.4 Hz, 1H), 3.31 (dd, J=18.1, 9.4 Hz, 1H), 2.68–2.42 (m, 10H), 2.34 (t, J=5.2 Hz, 1H), 2.25 (t, J=5.4 Hz, 1H), 1.49 (qt, J=7.3 Hz, 2H, 2′-H), 1.39 (s, 6H, two 6-Me groups), 1.35–1.28 (m, 4H, 3′-H, 4′-H), 1.01 (s, 3H, 6-Me), 0.99 (s, 3H, 6-Me), 0.89 (t, J=6.6 Hz, 3H, 5′-H). Mass spectrum m/z (relative intensity) 452 (M^+, 53), 409 (9), 382 (33), 358 (52), 335 (17), 304 (88), 273 (47), 233 (44), 83 (100). Exact mass calculated for $C_{29}H_{40}O_4$, 452.2926; found, 452.2915.

4.4. Conversion of byproduct 12 to 15a and isolation of hemiketal 13

A solution of **12** (17 mg, 0.047 mmol) and *p*-toluenesulfonic acid monohydrate (9 mg, 0.047 mmol) in $CHCl_3$ (2 mL) was stirred for 3.5 days under argon at room temperature. Workup of the reaction mixture as described for **15a** followed by preparative TLC purification (50% diethyl ether in hexane) gave **15a** (7 mg). Withdrawal of a sample of the reaction mixture after 2 days stirring followed by workup and preparative TLC purification (53% diethyl ether in hexane) afforded **15a** (2.7 mg) and **13** (2 mg, R_f=0.21, 65% diethyl ether in hexane). Compound **13**: pale yellow viscous oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.25 (d, J=2.5 Hz, 1H, ArH), 6.08 (d, J=2.5 Hz, 1H, ArH), 4.76 (br s, 1H, OH), 4.55 (br s, 1H, OH), 3.63 (t, J=7.9 Hz, 1H), 3.56 (dd, J=17.5, 9.0 Hz, 1H), 2.65 (d, J=11.0 Hz, 1H), 2.57 (t, J=5.0 Hz, 1H), 2.54–2.48 (m, 3H, especially 2.52, t, J=7.5 Hz, 2H, 1′-H), 2.43 (dd, J=17.5, 7.5 Hz, 1H), 2.16 (t, J=5.5 Hz, 1H), 1.55–1.47 (m, 2H, 2′-H), 1.37 (s, 3H, $>C(CH_3)_2$), 1.36–1.29 (m, 4H, 3′-H, 4′-H), 0.99 (s, 3H, $>C(CH_3)_2$), 0.90 (t, J=7.5 Hz, 3H, 5′-H).

4.5. (4*R*)-4-[4-(4′,4′,5′,5′,5′-$^2H_5$-Pentyl)-2,6-dihydroxyphenyl]-6,6-dimethyl-2-norpinanone (15b)

The synthesis was carried out as described for **15a** starting from **14b**[24,26] (4.202 g, 22.71 mmol), diacetates **8** (8.696 g, ca. 87% pure by ^{1}H NMR, 31.79 mmol), and *p*-toluenesulfonic acid monohydrate (6.040 g, 31.79 mmol) in $CHCl_3$ (227 mL) and gave 2.335 g (32%) of **15b** as a white solid. Mp=140–142 °C (from CH_2Cl_2/hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.17 (s, 2H, ArH), 5.27 (br s, 2H, OH), 3.95 (t, J=8.1 Hz, 1H), 3.49 (dd, J=18.8, 7.7 Hz, 1H), 2.63 (dd, J=18.8, 8.7 Hz, 1H), 2.59 (t, J=5.0 Hz, 1H), 2.51 (m, 1H), 2.46 (d, J=10.7 Hz, 1H), 2.42 (t, J=7.7 Hz, 2H, 1′-H), 2.30 (t, J=5.2 Hz, 1H), 1.54 (qt, J=7.7 Hz, 2H, 2′-H), 1.36 (s, 3H, 6-Me), 1.27 (t, J=7.6 Hz, 2H, 3′-H), 0.99 (s, 3H, 6-Me). Mass spectrum m/z (relative intensity) 321 (M^+, 88), 306 (29), 304 (18), 278 (57), 264 (12), 252 (24), 238 (87), 211 (36), 198 (61), 150 (37), 124 (81), 83 (100). Exact mass calculated for $C_{20}H_{23}D_5O_3$, 321.2352; found, 321.2348.

4.6. (4*R*)-4-[4-(5′,5′,5′-$^2H_3$-Pentyl)-2,6-dihydroxyphenyl]-6,6-dimethyl-2-norpinanone (15c)

The synthesis was carried out as described for **15a** starting from **14c**[24,26] (7.30 g, 39.83 mmol), diacetates **8** (13.273 g, ca. 87% pure by ^{1}H NMR, 55.77 mmol), and *p*-toluenesulfonic acid monohydrate (7.57 g, 39.83 mmol) in $CHCl_3$ (400 mL) and gave 3.955 g (31.1%) of **15c** as a white solid. Mp=141–143 °C (from CH_2Cl_2/hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.17 (s, 2H, ArH), 5.06 (br s, 2H, OH), 3.95 (t, J=8.1 Hz, 1H), 3.48 (dd, J=18.8, 7.7 Hz, 1H), 2.62 (dd, J=18.8, 8.6 Hz, 1H), 2.59 (t, J=5.1 Hz, 1H), 2.55–2.48 (m, 1H), 2.45 (d, J=10.7 Hz, 1H), 2.43 (t, J=7.8 Hz, 2H, 1′-H), 2.30 (t, J=5.2 Hz, 1H), 1.55 (qt, J=7.7 Hz, 2H, 2′-H), 1.36 (s, 3H, 6-Me), 1.33–1.27(m, 4H, 3′-H, 4′-H), 0.99 (s, 3H, 6-Me). Mass spectrum m/z (relative intensity) 319 (M^+, 84), 304 (29), 302 (17), 276 (60), 260 (18), 250 (38), 236 (100), 222 (46), 209 (41), 196 (70), 183 (32), 150 (67), 137 (30), 124 (98), 83 (91). Exact mass calculated for $C_{20}H_{25}D_3O_3$, 319.2223; found, 321.2226.

4.7. (4*R*)-4-[4-(2′,2′,3′,3′,3′-$^2H_5$-Propyl)-2,6-dihydroxyphenyl]-6,6-dimethyl-2-norpinanone (15d)

The synthesis was carried out as described for **15a** starting from **14d**[25] (7.30 g, 46.43 mmol), diacetates **8** (15.471 g, ca. 87% pure by ^{1}H NMR, 65.0 mmol), and

p-toluenesulfonic acid monohydrate (8.832 g, 46.43 mmol) in $CHCl_3$ (464 mL) and gave 4.25 g (31.2%) of **15d** as a white solid. Mp=156–157 °C (from CH_2Cl_2/hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.16 (s, 2H, ArH), 5.09 (br s, 2H, OH), 3.95 (t, J=8.0 Hz, 1H), 3.48 (dd, J=19.0, 8.0 Hz, 1H), 2.63 (dd, J=18.5, 9.0 Hz, 1H), 2.59 (t, J=5.0 Hz, 1H), 2.54–2.48 (m, 1H), 2.45 (d, J=11.0 Hz, 1H), 2.40 (s, 2H, 1′-H), 2.30 (t, J=5.5 Hz, 1H), 1.36 (s, 3H, 6-Me), 1.00 (s, 3H, 6-Me). Mass spectrum *m*/*z* (relative intensity) 293 (M^+, 100), 278 (22), 276 (14), 250 (52), 223 (20), 210 (66), 196 (30), 183 (55), 170 (42), 157 (16), 83 (39). Exact mass calculated for $C_{18}H_{19}D_5O_3$, 293.2042; found, 293.2039.

4.8. (4*R*)-4-[4-(3′,3′,3′-$^2H_3$-Propyl)-2,6-dihydroxyphenyl]-6,6-dimethyl-2-norpinanone (15e)

The synthesis was carried out as described for **15a** starting from **14e**[25] (3.554 g, 22.93 mmol), diacetates **8** (8.782 g, ca. 87% pure by ^{1}H NMR, 32.10 mmol), and *p*-toluenesulfonic acid monohydrate (6.099 g, 32.10 mmol) in $CHCl_3$ (230 mL) and gave 2.121 g (32%) of **15e** as a white solid. Mp=155–156 °C (from CH_2Cl_2/hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.17 (s, 2H, ArH), 5.19 (br s, 2H, OH), 3.95 (t, J=8.1 Hz, 1H), 3.49 (dd, J=18.9, 7.7 Hz, 1H), 2.63 (dd, J=18.9, 8.7 Hz, 1H), 2.59 (t, J=5.1 Hz, 1H), 2.51 (m, 1H), 2.45 (d, J=10.7 Hz, 1H), 2.41 (t, J=7.6 Hz, 2H, 1′-H), 2.30 (t, J=5.2 Hz, 1H), 1.56 (t, J=7.4 Hz, 2H, 2′-H), 1.36 (s, 3H, 6-Me), 0.99 (s, 3H, 6-Me). Mass spectrum *m*/*z* (relative intensity) 291 (M^+, 100), 276 (26), 274 (14), 248 (56), 234 (15), 222 (25), 208 (83), 194 (46), 181 (69), 168 (65), 83 (61). Exact mass calculated for $C_{18}H_{21}D_3O_3$, 291.1914; found, 291.1913.

4.9. (6a*R*,10a*R*)-6,6a,7,8,10,10a-Hexahydro-1-hydroxy-6,6-dimethyl-3-pentyl-9*H*-dibenzo[*b*,*d*]pyran-9-one (16a)

To a solution of **15a** (1.417 g, 4.48 mmol) in anhydrous CH_2Cl_2/CH_3NO_2 (3:1, 90 mL) at 0 °C, under an argon atmosphere was added trimethylsilyl trifluoromethanesulfonate (4.47 mL, 0.3 M solution in CH_3NO_2, 1.34 mmol) and the reaction mixture was stirred for 6 h. The reaction was quenched with saturated aqueous $NaHCO_3$/brine (1:1) and diethyl ether was added. The organic phase was separated, the aqueous phase was extracted with diethyl ether, the combined organic phase was washed with brine, and dried over $MgSO_4$. Solvent evaporation and purification by flash column chromatography on silica gel (50% diethyl ether in hexane) afforded 1.019 g (72% yield) of **16a**[29] as a white foam. R_f=0.29 (50% diethyl ether in hexane), R_f=0.43 (30% acetone in hexane). Mp=107–109 °C (lit.[29] 114–117 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.64 (br s, 1H, OH), 6.26 (s, 1H, 4-H), 6.21 (s, 1H, 2-H), 4.06 (d, J=15.0 Hz, 1H, 10α-H), 2.89 (td, J=12.1, 3.3 Hz, 1H, 8α-H), 2.66–2.60 (m, 1H, 8β-H), 2.51–2.39 (m, 1H, 7β-H and t, J=8.3 Hz, 2H, 1′-H overlapping), 2.20–2.11 (m, 2H, 10β-H, 10a-H), 1.97 (td, J=12.1, 2.4 Hz, 1H, 7α-H), 1.60–1.50 (m, 3H, 6a-H, 2′-H), 1.47 (s, 3H, 6β-Me), 1.35–1.25 (m, 4H, 3′-H, 4′-H), 1.12 (s, 3H, 6α-Me), 0.88 (t, J=6.8 Hz, 3H, 5′-H). Mass spectrum *m*/*z* (relative intensity) 316 (M^+, 100), 301 (30), 283 (10), 273 (22), 260 (44), 233 (67), 205 (30), 150 (37), 83 (23). Exact mass calculated for $C_{20}H_{28}O_3$, 316.2038; found, 316.2033.

4.10. (6a*R*,10a*R*)-6,6a,7,8,10,10a-Hexahydro-1-hydroxy-6,6-dimethyl-3-(4′,4′,5′,5′,5′-$^2H_5$-pentyl)-9*H*-dibenzo[*b*,*d*]-pyran-9-one (16b)

The synthesis was carried out as described for **16a** starting from **15b** (1.836 g, 5.72 mmol) and trimethylsilyl trifluoromethanesulfonate (5.73 mL, 0.3 M solution in CH_3NO_2, 1.72 mmol) in anhydrous CH_2Cl_2/CH_3NO_2 (3:1, 114 mL) and gave 1.330 g (72%) of **16b** as a white foam. Mp=108–110 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.02 (br s, 1H, OH), 6.25 (s, 1H, 4-H), 6.23 (s, 1H, 2-H), 4.09 (d, J=15.0 Hz, 1H, 10α-H), 2.89 (td, J=12.2, 3.3 Hz, 1H, 8α-H), 2.66–2.60 (m, 1H, 8β-H), 2.51–2.41 (m, 1H, 7β-H and t, J=8.4 Hz, 2H, 1′-H overlapping), 2.20–2.11 (m, 2H, 10β-H, 10a-H), 1.97 (td, J=12.1, 2.4 Hz, 1H, 7α-H), 1.60–1.50 (m, 3H, 6a-H, 2′-H), 1.47 (s, 3H, 6β-Me), 1.28 (t, J=7.6 Hz, 2H, 3′-H), 1.12 (s, 3H, 6α-Me). Mass spectrum *m*/*z* (relative intensity) 321 (M^+, 100), 306 (28), 304 (19), 288 (11), 278 (21), 260 (44), 238 (65), 205 (31), 150 (36), 83 (23). Exact mass calculated for $C_{20}H_{23}D_5O_3$, 321.2352; found, 321.2354.

4.11. (6a*R*,10a*R*)-6,6a,7,8,10,10a-Hexahydro-1-hydroxy-6,6-dimethyl-3-(5′,5′,5′-$^2H_3$-pentyl)-9*H*-dibenzo[*b*,*d*]-pyran-9-one (16c)

The synthesis was carried out as described for **16a** starting from **15c** (2.55 g, 7.98 mmol) and trimethylsilyl trifluoromethanesulfonate (7.98 mL, 0.3 M solution in CH_3NO_2, 2.394 mmol) in anhydrous CH_2Cl_2/CH_3NO_2 (3:1 mixture, 160 mL) and gave 1.810 g (71%) of **16c** as a white foam. Mp=108–110 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.11 (br s, 1H, OH), 6.25 (s, 1H, 4-H), 6.23 (s, 1H, 2-H), 4.10 (d, J=15.0 Hz, 1H, 10α-H), 2.89 (td, J=12.0, 3.5 Hz, 1H, 8α-H), 2.66–2.60 (m, 1H, 8β-H), 2.51–2.41 (m, 1H, 7β-H and t, J=8.5 Hz, 2H, 1′-H overlapping), 2.20–2.11 (m, 2H, 10β-H, 10a-H), 1.97 (td, J=12.0, 2.5 Hz, 1H, 7α-H), 1.59–1.50 (m, 3H, 6a-H, 2′-H), 1.47(s, 3H, 6β-Me), 1.32–1.26 (m, 4H, 3′-H, 4′-H), 1.12 (s, 3H, 6α-Me). Mass spectrum *m*/*z* (relative intensity) 319 (M^+, 20), 304 (7), 276 (5), 260 (14), 236 (16), 220 (28), 205 (100), 150 (15), 124 (25), 69 (14), 57 (25). Exact mass calculated for $C_{20}H_{25}D_3O_3$, 319.2228; found, 319.2226.

4.12. (6a*R*,10a*R*)-6,6a,7,8,10,10a-Hexahydro-1-hydroxy-6,6-dimethyl-3-(2′,2′,3′,3′,3′-$^2H_5$-propyl)-9*H*-dibenzo[*b*,*d*]-pyran-9-one (16d)

The synthesis was carried out as described for **16a** starting from **15d** (2.43 g, 8.28 mmol) and trimethylsilyl trifluoromethanesulfonate (8.28 mL, 0.3 M solution in CH_3NO_2, 2.484 mmol) in anhydrous CH_2Cl_2/CH_3NO_2 (3:1 mixture, 165 mL) and gave 1.72 g (70%) of **16d** as a white foam. Mp=120–122 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.44 (br s, 1H, OH), 6.26 (d, J=1.5 Hz, 1H, 4-H), 6.19 (d, J=1.5 Hz, 1H, 2-H), 4.04 (ddd, J=15.0, 4.0, 2.5 Hz 1H, 10α-H), 2.89 (td, J=12.0, 4.0 Hz, 1H, 8α-H), 2.65–2.59 (m, 1H, 8β-H), 2.52–2.40 (m, 1H, 7β-H and s, 2H, 1′-H overlapping), 2.20–2.11 (m, 2H, 10β-H, 10a-H), 1.96 (td, J=12.0, 2.5 Hz, 1H, 7α-H), 1.56–1.48 (m, 1H, 6a-H), 1.47(s, 3H, 6β-Me), 1.12 (s, 3H, 6α-Me). Mass spectrum *m*/*z* (relative intensity) 293 (M^+, 100), 278 (40), 276 (20), 260 (17), 250 (26), 245 (19), 222 (16), 210 (88), 183 (57),

170 (24), 151 (16), 91 (11). Exact mass calculated for $C_{18}H_{19}D_5O_3$, 293.2038; found, 293.2039.

4.13. (6a*R*,10a*R*)-6,6a,7,8,10,10a-Hexahydro-1-hydroxy-6,6-dimethyl-3-(3′,3′,3′-$^2H_3$-propyl)-9*H*-dibenzo[*b*,*d*]-pyran-9-one (16e)

The synthesis was carried out as described for **16a** starting from **15e** (1.967 g, 6.76 mmol) and trimethylsilyl trifluoromethanesulfonate (6.77 mL, 0.3 M solution in CH_3NO_2, 2.03 mmol) in anhydrous CH_2Cl_2/CH_3NO_2 (3:1, 135 mL) and gave 1.348 g (69%) of **16e** as a white foam. Mp=118–120 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.78 (br s, 1H, OH), 6.25 (s, 1H, 4-H), 6.21 (s, 1H, 2-H), 4.07 (d, J=15.0 Hz, 1H, 10α-H), 2.89 (td, J=12.2, 3.4 Hz, 1H, 8α-H), 2.65–2.60 (m, 1H, 8β-H), 2.52–2.41 (m, 1H, 7β-H and t, J=8.4 Hz, 2H, 1′-H overlapping), 2.20–2.11 (m, 2H, 10β-H, 10a-H), 1.97 (td, J=12.2, 2.6 Hz, 1H, 7α-H), 1.58–1.49 (m, 1H, 6a-H and t, J=7.2 Hz, 2H, 2′-H overlapping), 1.47 (s, 3H, 6β-Me), 1.12 (s, 3H, 6α-Me). Mass spectrum m/z (relative intensity) 291 (M^+, 100), 276 (37), 274 (19), 258 (15), 248 (22), 245 (20), 220 (15), 208 (73), 181 (49), 168 (21), 83 (11). Exact mass calculated for $C_{18}H_{21}D_3O_3$, 291.1914; found, 291.1908.

4.14. 2,4,6-Triisopropylbenzenesulfonylhydrazone (trisylhydrazone) 17a

Ketone **16a** (0.731 g, 2.31 mmol) and 2,4,6-triisopropylbenzenesulfonylhydrazide (0.689 g, 2.31 mmol) were mixed in anhydrous benzene (115 mL) and the solvent was evaporated under reduced pressure (10–15 min) at 40–42 °C to give **17a** as a foam [mp=73–77 °C (dec)] along with traces of uncharacterized impurities. This material (1.38 g) was used into the next step without further purification. On the basis of ^{1}H NMR analysis, **17a** is a mixture of two isomeric trisylhydrazones **17a$_1$** (R_f=0.65, 35% ethyl acetate in hexane) and **17a$_2$** (R_f=0.59, 35% ethyl acetate in hexane) in a ratio 2.7:1, respectively. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.18 (s, 2H, ArH, tris-group, **17a$_2$**), 7.17 (s, 2H, ArH, tris-group, **17a$_1$**), 6.26 (d, J=1.5 Hz, 1H, 4-H, **17a$_1$**), 6.24 (d, J=1.5 Hz, 1H, 4-H, **17a$_2$**), 6.14 (d, J=1.5 Hz, 1H, 2-H, **17a$_1$**), 6.07 (d, J=1.5 Hz, 1H, 2-H, **17a$_2$**), 4.29–4.19 (m, 2H, *o*-C*H*$(CH_3)_2$, **17a$_1$** and 2H, *o*-C*H*$(CH_3)_2$, **17a$_2$**), 4.10 (dd, J=14.6, 2.4 Hz, 1H, 10α-H, **17a$_1$**), 3.88 (br d, J=14.5 Hz, 1H, 10α-H, **17a$_2$**), 2.94–2.87 (m, 1H, *p*-C*H*$(CH_3)_2$, **17a$_1$** and 1H, *p*-C*H*$(CH_3)_2$, **17a$_2$**), 2.85–1.50 (m, 8α-H, 8β-H, 7β-H, 1′-H, 10β-H, 10a-H, 7α-H, 6a-H, 2′-H, overlapping, **17a$_1$** and **17a$_2$**), 1.40 (s, 3H, 6β-Me, **17a$_2$**), 1.37 (s, 3H, 6β-Me, **17a$_1$**), 1.34–1.22 (m, *o*-CH$(CH_3)_2$, *p*-CH$(CH_3)_2$, 3′-H, 4′-H, overlapping, **17a$_1$** and **17a$_2$**), 1.04 (s, 3H, 6α-Me, **17a$_2$**), 1.03 (s, 3H, 6α-Me, **17a$_1$**), 0.88 (t, J=6.7 Hz, 3H, 5′-H, **17a$_1$**), 0.87 (t, J=6.7 Hz, 3H, 5′-H, **17a$_2$**).

4.15. 2,4,6-Triisopropylbenzenesulfonylhydrazone (trisylhydrazone) 17b

The synthesis was carried out as described for **17a** starting from **16b** (0.924 g, 2.88 mmol) and 2,4,6-triisopropylbenzenesulfonylhydrazide (0.858 g, 2.88 mmol) in anhydrous benzene (144 mL) and gave 1.730 g of **17b** as a foam, which was used into the next step without further purification.

4.16. 2,4,6-Triisopropylbenzenesulfonylhydrazone (trisylhydrazone) 17c

The synthesis was carried out as described for **17a** starting from **16c** (1.6 g, 5.0 mmol) and 2,4,6-triisopropylbenzenesulfonylhydrazide (1.495 g, 5.00 mmol) in anhydrous benzene (250 mL) and gave 3.00 g of **17c** as a foam, which was used into the next step without further purification.

4.17. 2,4,6-Triisopropylbenzenesulfonylhydrazone (trisylhydrazone) 17d

The synthesis was carried out as described for **17a** starting from **16d** (1.10 g, 3.75 mmol) and 2,4,6-triisopropylbenzenesulfonylhydrazide (1.017 g, 3.75 mmol) in anhydrous benzene (188 mL) and gave 2.151 g of **17d** as a foam, which was used into the next step without further purification.

4.18. 2,4,6-Triisopropylbenzenesulfonylhydrazone (trisylhydrazone) 17e

The synthesis was carried out as described for **17a** starting from **16e** (0.850 g, 2.92 mmol) and 2,4,6-triisopropylbenzenesulfonylhydrazide (0.870 g, 2.92 mmol) in anhydrous benzene (146 mL) and gave 1.668 g of **17e** as a foam, which was used into the next step without further purification.

4.19. (6a*R*,10a*R*)-6a,7,8,10a-Tetrahydro-1-hydroxy-6,6-dimethyl-3-pentyl-6*H*-dibenzo[*b*,*d*]pyran-9-carboxylic acid (1h)

To a solution of trisylhydrazone **17a** (1.38 g, 2.31 mmol) in dry hexane/TMEDA (77 mL, 1:1 ratio) under an argon atmosphere at −78 °C was added *n*-BuLi (2.12 mL, 5.31 mmol, using a 2.5 M solution in hexane). The reaction mixture was stirred for 20 min at −78 °C, and then it was warmed to −5 °C over a 10 min period and stirred at that temperature for an additional 20 min. The reaction mixture was cooled to −78 °C and a second portion of *n*-BuLi (2.12 mL, 5.31 mmol) was added. Following the addition, the mixture was stirred for 10 min at −78 °C and then allowed to warm to −5 °C over a 10 min period. Stirring was continued for 20 min at −5 to 0 °C and then dry CO_2 was bubbled into the reaction mixture for 10 min. The pH was adjusted to 2 by the addition of 5% aqueous HCl solution at 0 °C, and the mixture was warmed to room temperature and extracted with diethyl ether. The ethereal solution was washed with brine, dried ($MgSO_4$), and the solvent was evaporated under reduced pressure. The residue obtained was purified by flash column chromatography on silica gel to give a mixture of **24**[51] and **25**[52] as a pale yellow gum (119 mg, 17% yield, eluted by 15% ethyl acetate in hexane, ratio of **24/25** (89:11) on the basis of ^{1}H NMR analysis) as well as a mixture of **1h** and **2h** as a pale yellow semisolid material (398 mg, 50% yield, eluted by 45% ethyl acetate in hexane, ratio of **1h/2h** (89:11) on the basis of ^{1}H NMR analysis). Recrystallization of this mixture from chloroform gave pure **1h**[2,11,19,29] [183 mg, 23% yield from **16a**, 99% free from **2h**[4] based on ^{1}H NMR data: [7.10 (m, 8-H), 3.88 (br d, 10α-H), 2.68 (td, 10a-H) for **2h**] as a white solid. Mp=216–218 °C [lit.[29] 206–209 °C, lit.[19] 202–203.5 °C (dec)]. *Mixture of **24** and **25***: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.61 (dq, J=10.5, 2.5 Hz, 1H, 10-H, **24**), 6.27 (d,

J=1.5 Hz, 1H, 4-H, **24** and d, J=1.5 Hz, 1H, 4-H, **25**, overlapping), 6.12 (d, J=1.5 Hz, 1H, 2-H, **24**), 6.10 (d, J=1.5 Hz, 1H, 2-H, **25**), 5.78–5.70 (m, 2H, 8-H, 9-H, **25**), 5.66 (dq, J=9.5, 3.5 Hz, 1H, 9-H, **24**), 4.74 (br s, 2H, OH, **24** and **25**), 3.33 (dt, J=16.5, 2.3 Hz, 1H, 10α-H, **25**), 3.25 (br d, J=10.8 Hz, 1H, 10a-H, **24**), 2.71 (ddd as td, J=10.6, 4.6 Hz, 1H, 10a-H, **25**), 2.44 (t, J=7.6 Hz, 4H, 1′-H, **24** and **25**, overlapping), 2.32–2.15 (m, 3H, 8α-H, 8β-H, **24** and 7α-H, **25**, overlapping), 1.94–1.84 (m, 4H, 7-H, **24** and 7β-H, 10β-H, 6a-H, **25**, overlapping), 1.75 (td, J=11.2, 1.4 Hz, 1H, 6a-H, **24**), 1.56 (qt, J=7.2 Hz, 4H, 2′-H, **24** and **25**, overlapping), 1.45–1.39 (m, 4H, 7-H, 6β-Me, **24**, especially 1.41, s, 6β-Me), 1.38 (s, 3H, 6β-Me, **25**), 1.35–1.22 (m, 8H, 3′-H, 4′-H, **24** and **25**, overlapping), 1.11 (s, 3H, 6α-Me, **25**), 1.10 (s, 3H, 6α-Me, **24**), 0.88 (t, J=7.1 Hz, 6H, 5′-H, **24** and **25**, overlapping). Compound **1h**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13 (m as d, J=1.8 Hz, 1H, 10-H), 6.40 (br s, 1H, OH), 6.25 (d, J=1.0 Hz, 1H, 4-H), 6.20 (d, J=1.0 Hz, 1H, 2-H), 3.39 (br d, J=11.1 Hz, 1H, 10a-H), 2.60–2.54 (m, 1H, 8-H), 2.50–2.39 (m, 3H, 8-H and 1′-H, overlapping), 2.06–1.99 (m, 1H, 7-H), 1.74 (t, J=11.7 Hz, 1H, 6a-H), 1.56 (qt, J=7.6 Hz, 2H, 2′-H), 1.48–1.37 (m, 4H, 7-H, 6β-Me, especially 1.44, s, 6β-Me), 1.35–1.23 (m, 4H, 3′-H, 4′-H), 1.12 (s, 3H, 6α-Me), 0.88 (t, J=6.9 Hz, 3H, 5′-H). Mass spectrum m/z (relative intensity) 344 (M^+, 100), 329 (78), 299 (92), 288 (54). Exact mass calculated for $C_{21}H_{28}O_4$, 344.1988; found, 344.1983.

4.20. (6a*R*,10a*R*)-6a,7,8,10a-Tetrahydro-1-hydroxy-6,6-dimethyl-3-(4′,4′,5′,5′,5′-$^2H_5$-pentyl)-6*H*-dibenzo[*b*,*d*]-pyran-9-carboxylic acid (18b)

The synthesis was carried out as described for **1h** starting from **17b** (1.730 g, 2.88 mmol) and *n*-BuLi (5.3 mL, 13.24 mmol, using a 2.5 M solution in hexane) in dry hexane/TMEDA (96 mL, 1:1 ratio) and gave a mixture of **18b** and **19b** as a pale yellow semisolid material [510 mg, 51% yield, eluted by 45% ethyl acetate in hexane, ratio of **18b/19b** (87:13) on the basis of ^{1}H NMR analysis]. Recrystallization of this mixture from chloroform gave pure **18b** (235 mg, 23% yield from **16b**) as a white solid. Mp=215–217 °C; ^{1}H NMR (500 MHz, $CDCl_3$+CD_3COCD_3) δ 8.11 (m as d, J=1.8 Hz, 1H, 10-H), 6.26 (d, J=1.0 Hz, 1H, 4-H), 6.19 (d, J=1.0 Hz, 1H, 2-H), 6.08 (br s, 1H, OH), 3.39 (br d, J=11.2 Hz, 1H, 10a-H), 2.60–2.54 (m, 1H, 8-H), 2.50–2.39 (m, 3H, 8-H and 1′-H, overlapping), 2.06–1.99 (m, 1H, 7-H), 1.74 (t, J=11.8 Hz, 1H, 6a-H), 1.55 (qt, J=7.7 Hz, 2H, 2′-H), 1.47–1.37 (m, 4H, 7-H, 6β-Me, especially 1.44, s, 6β-Me), 1.27 (t, J=7.6 Hz, 2H, 3′-H), 1.12 (s, 3H, 6α-Me). Mass spectrum m/z (relative intensity) 349 (M^+, 82), 334 (56), 304 (81), 288 (31), 260 (21), 236 (16), 223 (45), 205 (100), 168 (47), 141 (49), 115 (56), 91 (39), 77 (91). Exact mass calculated for $C_{21}H_{23}D_5O_4$, 349.2301; found, 349.2300. The deuterium incorporation on the molecular ion cluster using FI was $^2H_5$: 97.1%, $^2H_4$: 2.2%, and $^2H_3$: 0.7%.

4.21. (6a*R*,10a*R*)-6a,7,8,10a-Tetrahydro-1-hydroxy-6,6-dimethyl-3-(5′,5′,5′-$^2H_3$-pentyl)-6*H*-dibenzo[*b*,*d*]pyran-9-carboxylic acid (18c)

The synthesis was carried out as described for **1h** starting from **17c** (1.127 g, 1.88 mmol) and *n*-BuLi (3.46 mL, 8.64 mmol, using a 2.5 M solution in hexane) in dry hexane/TMEDA (64 mL, 1:1 ratio) and gave a mixture of **18c** and **19c** as a pale yellow semisolid material (320 g, 49% yield, eluted by 45% ethyl acetate in hexane, **18c/19c** (85:15) on the basis of ^{1}H NMR analysis). Recrystallization of this mixture from chloroform gave pure **18c** (137 mg, 21% yield from **16c**) as a white solid. Mp=216–218 °C; ^{1}H NMR (500 MHz, $CDCl_3$+CD_3COCD_3) δ 8.11 (br s, 1H, 10-H), 6.60 (br s, 1H, OH), 6.25 (d, J=1.0 Hz, 1H, 4-H), 6.21 (d, J=1.0 Hz, 1H, 2-H), 3.39 (br d, J=11.0 Hz, 1H, 10a-H), 2.62–2.52 (m, 1H, 8-H), 2.50–2.38 (m, 3H, 8-H and 1′-H, overlapping), 2.06–1.98 (m, 1H, 7-H), 1.74 (t, J=11.5 Hz, 1H, 6a-H), 1.56 (qt, J=7.5 Hz, 2H, 2′-H), 1.48–1.37 (m, 4H, 7-H, 6β-Me, especially 1.44, s, 6β-Me), 1.34–1.20 (m, 4H, 3′-H, 4′-H), 1.12 (s, 3H, 6α-Me). Mass spectrum m/z (relative intensity) 347 (M^+, 100), 332 (71), 302 (95), 288 (25), 279 (21), 220 (14), 196 (17), 174 (11). Exact mass calculated for $C_{21}H_{25}D_3O_4$, 347.2179; found, 347.2176. The deuterium incorporation on the molecular ion cluster using FI was $^2H_3$: 96.4%, $^2H_2$: 2.2%, $^2H_1$: 1.0%, and $^2H_0$: 0.4%.

4.22. (6a*R*,10a*R*)-6a,7,8,10a-Tetrahydro-1-hydroxy-6,6-dimethyl-3-(2′,2′,3′,3′,3′-$^2H_5$-propyl)-6*H*-dibenzo[*b*,*d*]-pyran-9-carboxylic acid (18d)

The synthesis was carried out as described for **1h** starting from **17d** (2.1 g, 3.66 mmol) and *n*-BuLi (6.73 mL, 16.83 mmol, using a 2.5 M solution in hexane) in dry hexane/TMEDA (122 mL, 1:1) and gave a mixture of **18d** and **19d** as a pale yellow semisolid material [600 mg, 51% yield, eluted by 45% ethyl acetate in hexane, **18d/19d** (87:13) on the basis of ^{1}H NMR analysis]. Recrystallization of this mixture from chloroform/hexane gave pure **18d** (270 mg, 23% yield from **16d**) as a white solid. Mp=161–163 °C; ^{1}H NMR (500 MHz, $CDCl_3$+CD_3COCD_3) δ 8.14 (m as d, J=2.0 Hz, 1H, 10-H), 6.62 (br s, 1H, OH), 6.24 (d, J=1.5 Hz, 1H, 4-H), 6.21 (d, J=1.5 Hz, 1H, 2-H), 3.39 (br d, J=11.5 Hz, 1H, 10a-H), 2.61–2.52 (m, 1H, 8-H), 2.48–2.36 (m, 3H, 8-H, 1′-H especially 2.40, s, 1′-H), 2.06–1.98 (m, 1H, 7-H), 1.74 (td, J=12.0, 2.0 Hz, 1H, 6a-H), 1.47–1.37 (m, 4H, 7-H, 6β-Me, especially 1.42, s, 6β-Me), 1.12 (s, 3H, 6α-Me). Mass spectrum m/z (relative intensity) 321 (M^+, 100), 306 (74), 276 (98), 260 (26), 208 (27), 170 (27), 115 (11), 69 (13). Exact mass calculated for $C_{19}H_{19}D_5O_4$, 321.1985; found, 321.1988. The deuterium incorporation on the molecular ion cluster using FI was $^2H_5$: 96.8%, $^2H_4$: 1.9%, $^2H_3$: 0.7%, and $^2H_1$: 0.6%.

4.23. (6a*R*,10a*R*)-6a,7,8,10a-Tetrahydro-1-hydroxy-6,6-dimethyl-3-(3′,3′,3′-$^2H_3$-propyl)-6*H*-dibenzo[*b*,*d*]pyran-9-carboxylic acid (18e)

The synthesis was carried out as described for **1h** starting from **17e** (1.668 g, 2.92 mmol) and *n*-BuLi (5.38 mL, 13.44 mmol, using a 2.5 M solution in hexane) in dry hexane/TMEDA (97 mL, 1:1 ratio) and gave a mixture of **18e** and **19e** as a pale yellow semisolid material [468 mg, 50% yield, eluted by 45% ethyl acetate in hexane, **18e/19e** (86:14) on the basis of ^{1}H NMR analysis]. Recrystallization of this mixture from chloroform/hexane gave pure **18e** (209 mg, 22% yield from **16e**) as a white solid. Mp=161–163 °C; ^{1}H NMR (500 MHz, $CDCl_3$+CD_3COCD_3) δ 8.13 (m as d, J=1.7 Hz, 1H, 10-H), 6.42 (br s, 1H, OH), 6.25

(d, J=1.0 Hz, 1H, 4-H), 6.20 (d, J=1.0 Hz, 1H, 2-H), 3.39 (br d, J=11.0 Hz, 1H, 10a-H), 2.60–2.54 (m, 1H, 8-H), 2.48–2.38 (m, 3H, 8-H and 1′-H, overlapping), 2.06–1.98 (m, 1H, 7-H), 1.74 (t, J=11.6 Hz, 1H, 6a-H), 1.56 (t, J=7.4 Hz, 2H, 2′-H), 1.47–1.37 (m, 4H, 7-H, 6β-Me, especially 1.44, s, 6β-Me), 1.12 (s, 3H, 6α-Me). Mass spectrum *m/z* (relative intensity) 319 (M^+, 35), 304 (27), 291 (7), 274 (36), 258 (9), 205 (10), 168 (7), 84 (34), 58 (100). Exact mass calculated for $C_{19}H_{21}D_3O_4$, 319.1863; found, 319.1861. The deuterium incorporation on the molecular ion cluster using FI was $^2H_3$: 97.4%, $^2H_2$: 1.7%, and $^2H_1$: 0.9%.

4.24. (6a*R*,10a*R*)-6a,7,8,10a-Tetrahydro-1-hydroxy-6,6-dimethyl-3-(4′,4′,5′,5′,5′-$^2H_5$-pentyl)-6*H*-dibenzo[*b*,*d*]-pyran-9-carboxylic acid methyl ester (20b)

Diazomethane solution in diethyl ether (~2.8 g in 100 mL) was prepared according to a reported procedure.[50] To a stirred solution of **18b** (218 mg, 0.62 mmol) in diethyl ether (25 mL) at 0 °C was added dropwise an ethereal solution of diazomethane until the TLC analysis indicated the total consumption of the starting material (30 min). Then, solid $MgSO_4$ was added, stirring was continued for 5 min, and insoluble materials were filtered off. Evaporation of the solvent left the title compound **20b** as a white foam in quantitative yield (226 mg). ^1H NMR (500 MHz, $CDCl_3$) δ 7.97 (m as q, J=2.0 Hz, 1H, 10-H), 6.27 (d, J=1.5 Hz, 1H, 4-H), 6.15 (d, J=1.5 Hz, 1H, 2-H), 5.13 (br s, 1H, OH), 3.73 (s, 3H, $COOCH_3$), 3.36 (br d, J=11.3 Hz, 1H, 10a-H), 2.60–2.54 (m, 1H, 8-H), 2.49–2.40 (m, 3H, 8-H and 1′-H, overlapping), 2.04–1.98 (m, 1H, 7-H), 1.72 (td, J=11.9, 2.0 Hz, 1H, 6a-H), 1.55 (qt, J=7.8 Hz, 2H, 2′-H), 1.46–1.37 (m, 4H, 7-H, 6β-Me, especially 1.44, s, 6β-Me), 1.27 (t, J=7.7 Hz, 2H, 3′-H), 1.12 (s, 3H, 6α-Me). Mass spectrum *m/z* (relative intensity) 363 (M^+, 45), 348 (87), 320 (17), 304 (100), 288 (26), 263 (13), 236 (20). Exact mass calculated for $C_{22}H_{25}D_5O_4$, 363.2458; found, 363.2456.

4.25. (6a*R*,10a*R*)-6a,7,8,10a-Tetrahydro-1-hydroxy-6,6-dimethyl-3-(5′,5′,5′-$^2H_3$-pentyl)-6*H*-dibenzo[*b*,*d*]pyran-9-carboxylic acid methyl ester (20c)

The synthesis was carried out as described for **20b** starting from **18c** (160 mg, 0.46 mmol) to give **20c** in quantitative yield (166 mg) as a white foam. ^1H NMR (500 MHz, $CDCl_3$) δ 8.02 (m as q, J=2.0 Hz, 1H, 10-H), 6.27 (d, J=1.5 Hz, 1H, 4-H), 6.19 (d, J=1.5 Hz, 1H, 2-H), 5.36 (br s, 1H, OH), 3.76 (s, 3H, $COOCH_3$), 3.37 (br d, J=11.5 Hz, 1H, 10a-H), 2.62–2.52 (m, 1H, 8-H), 2.50–2.40 (m, 3H, 8-H and 1′-H, overlapping), 2.04–1.98 (m, 1H, 7-H), 1.72 (td, J=12.0, 2.0 Hz, 1H, 6a-H), 1.55 (qt, J=7.5 Hz, 2H, 2′-H), 1.46–1.37 (m, 4H, 7-H, 6β-Me, especially 1.43, s, 6β-Me), 1.34–1.24 (m, 4H, 3′-H, 4′-H), 1.12 (s, 3H, 6α-Me). Mass spectrum *m/z* (relative intensity) 361 (M^+, 43), 346 (83), 318 (15), 302 (100). Exact mass calculated for $C_{22}H_{27}D_3O_4$, 361.2332; found, 361.2328.

4.26. (6a*R*,10a*R*)-6a,7,8,10a-Tetrahydro-1-hydroxy-6,6-dimethyl-3-(2′,2′,3′,3′,3′-$^2H_5$-propyl)-6*H*-dibenzo[*b*,*d*]-pyran-9-carboxylic acid methyl ester (20d)

The synthesis was carried out as described for **20b** starting from **18d** (160 mg, 0.5 mmol) and gave **20d** in quantitative yield (167 mg) as a white foam. ^1H NMR (500 MHz, $CDCl_3$) δ 7.97 (m as q, J=2.0 Hz, 1H, 10-H), 6.27 (d, J=1.5 Hz, 1H, 4-H), 6.14 (d, J=1.5 Hz, 1H, 2-H), 5.11 (br s, 1H, OH), 3.74 (s, 3H, $COOCH_3$), 3.36 (br d, J=11.0 Hz, 1H, 10a-H), 2.60–2.54 (m, 1H, 8-H), 2.49–2.39 (m, 3H, 8-H and 1′-H, especially 2.41, s, 1′-H), 2.04–1.98 (m, 1H, 7-H), 1.73 (td, J=12.0, 2.0 Hz, 1H, 6a-H), 1.46–1.36 (m, 4H, 7-H, 6β-Me, especially 1.44, s, 6β-Me), 1.12 (s, 3H, 6α-Me). Mass spectrum *m/z* (relative intensity) 335 (M^+, 45), 320 (80), 292 (17), 276 (100). Exact mass calculated for $C_{20}H_{21}D_5O_4$, 335.2145; found, 335.2139.

4.27. (6a*R*,10a*R*)-6a,7,8,10a-Tetrahydro-1-hydroxy-6,6-dimethyl-3-(3′,3′,3′-$^2H_3$-propyl)-6*H*-dibenzo[*b*,*d*]pyran-9-carboxylic acid methyl ester (20e)

The synthesis was carried out as described for **20b** starting from **18e** (164 mg, 0.514 mmol) and gave **20e** in quantitative yield (171 mg) as a white foam. ^1H NMR (500 MHz, $CDCl_3$) δ 7.97 (m as q, J=1.9 Hz, 1H, 10-H), 6.27 (d, J=1.5 Hz, 1H, 4-H), 6.14 (d, J=1.5 Hz, 1H, 2-H), 5.05 (br s, 1H, OH), 3.73 (s, 3H, $COOCH_3$), 3.36 (br d, J=11.1 Hz, 1H, 10a-H), 2.60–2.54 (m, 1H, 8-H), 2.49–2.39 (m, 3H, 8-H and 1′-H, overlapping), 2.04–1.98 (m, 1H, 7-H), 1.72 (td, J=11.8, 1.9 Hz, 1H, 6a-H), 1.57 (t, J=7.6 Hz, 2H, 2′-H), 1.46–1.37 (m, 4H, 7-H, 6β-Me, especially 1.43, s, 6β-Me), 1.12 (s, 3H, 6α-Me). Mass spectrum *m/z* (relative intensity) 333 (M^+, 49), 318 (82), 290 (23), 274 (100), 258 (35), 233 (29), 206 (35). Exact mass calculated for $C_{20}H_{23}D_3O_4$, 333.2019; found, 333.2024.

4.28. (6a*R*,10a*R*)-6a,7,8,10a-Tetrahydro-1-hydroxy-6,6-dimethyl-3-(4′,4′,5′,5′,5′-$^2H_5$-pentyl)-6*H*-dibenzo[*b*,*d*]-pyran-9-methanol (21b)

To a solution of **20b** (205 mg, 0.56 mmol) in anhydrous CH_2Cl_2 (8 mL) at −78 °C under an argon atmosphere was added diisobutylaluminum hydride (1.68 mL, 1 M solution in toluene) over a period of 15 min. The reaction mixture was stirred at the same temperature for 20 min and then quenched by dropwise addition of potassium sodium tartrate (10% solution in water). The mixture was warmed to room temperature, stirred vigorously for 40 min, and then diluted with ethyl acetate. The organic phase was separated and the aqueous phase extracted with ethyl acetate. The combined organic layer was washed with brine, dried over $MgSO_4$, and the solvent was evaporated under reduced pressure. The product was purified by flash column chromatography on silica gel using 45% ethyl acetate in hexane as an eluent to give compound **21b** as a white solid in 97% yield (184 mg). Mp 140–141 °C; ^1H NMR (500 MHz, $CDCl_3$+CD_3COCD_3) δ 6.72 (m as d, J=1.5 Hz, 1H, 10-H), 6.24 (d, J=1.5 Hz, 1H, 4-H), 6.17 (d, J=1.5 Hz, 1H, 2-H), 6.13 (s, 1H, OH), 4.03 (br s, 2H, 11-H), 3.26 (br d, J=11.1 Hz, 1H, 10a-H), 2.46–2.37 (m as td, J=7.8, 2.2 Hz, 2H, 1′-H), 2.35–2.29 (m, 1H, 8-H), 2.29–2.20 (m, 1H, 8-H), 2.01–1.95 (m, 1H, 7-H), 1.71 (td, J=11.8, 1.9 Hz, 1H, 6a-H), 1.59 (br s, 1H, OH), 1.55 (qt, J=7.7 Hz, 2H, 2′-H), 1.47–1.36 (m, 4H, 7-H, 6β-Me, especially 1.42, s, 6β-Me), 1.27 (t, J=7.7 Hz, 2H, 3′-H), 1.11 (s, 3H, 6α-Me). Mass spectrum *m/z* (relative intensity) 335 (M^+, 21), 317 (9), 304 (100), 236 (11), 198 (12). Exact mass calculated for $C_{21}H_{25}D_5O_3$, 335.2509; found,

335.2502. The deuterium incorporation on the molecular ion cluster using FI was $^2H_5$: 97.6%, $^2H_4$: 1.9%, and $^2H_3$: 0.5%.

4.29. (6a*R*,10a*R*)-6a,7,8,10a-Tetrahydro-1-hydroxy-6,6-dimethyl-3-(5′,5′,5′-$^2H_3$-pentyl)-6*H*-dibenzo[*b*,*d*]pyran-9-methanol (21c)

The synthesis was carried out as described for **21b** starting from **20c** (145 mg, 0.4 mmol) and diisobutylaluminum hydride (1.2 mL, 1 M solution in toluene) in anhydrous CH_2Cl_2 (7 mL) and gave 130 mg (95.8%) of **21c** as a white solid. Mp=139–141 °C; ^1H NMR (500 MHz, $CDCl_3$+CD_3COCD_3) δ 6.72 (m as d, J=1.5 Hz, 1H, 10-H), 6.42 (s, 1H, OH), 6.24 (d, J=1.5 Hz, 1H, 4-H), 6.19 (d, J=1.5 Hz, 1H, 2-H), 4.03 (br s, 2H, 11-H), 3.26 (br d, J=11.0 Hz, 1H, 10a-H), 2.45–2.40 (m as td, J=8.0, 2.0 Hz, 2H, 1′-H), 2.36–2.29 (m, 1H, 8-H), 2.29–2.20 (m, 1H, 8-H), 2.01–1.95 (m as dd, J=12.0, 7.0 Hz, 1H, 7-H), 1.94 (br s, 1H, OH), 1.71 (td, J=11.5, 2.0 Hz, 1H, 6a-H), 1.55 (qt, J=8.0 Hz, 2H, 2′-H), 1.47–1.36 (m, 4H, 7-H, 6β-Me, especially 1.42, s, 6β-Me), 1.32–1.22 (m, 4H, 3′-H, 4′-H), 1.11 (s, 3H, 6α-Me). Mass spectrum *m*/*z* (relative intensity) 333 (M^+, 20), 315 (7), 302 (100). Exact mass calculated for $C_{21}H_{27}D_3O_3$, 333.2383; found, 333.2378. The deuterium incorporation on the molecular ion cluster using FI was $^2H_3$: 96.2%, $^2H_2$: 2.1%, $^2H_1$: 1.0%, and $^2H_0$: 0.7%.

4.30. (6a*R*,10a*R*)-6a,7,8,10a-Tetrahydro-1-hydroxy-6,6-dimethyl-3-(2′,2′,3′,3′,3′-$^2H_5$-propyl)-6*H*-dibenzo[*b*,*d*]-pyran-9-methanol (21d)

The synthesis was carried out as described for **21b** starting from **20d** (140 mg, 0.42 mmol) and diisobutylaluminum hydride (1.25 mL, 1 M solution in toluene) in anhydrous CH_2Cl_2 (7 mL) and gave 120 mg (94%) of **21d** as a white solid. Mp=135–136 °C; ^1H NMR (500 MHz, $CDCl_3$+CD_3COCD_3) δ 6.72 (m as d, J=1.5 Hz, 1H, 10-H), 6.24 (d, J=1.5 Hz, 1H, 4-H), 6.17 (d, J=1.5 Hz, 1H, 2-H), 6.08 (br s, 1H, OH), 4.03 (br s, 2H, 11-H), 3.26 (br d, J=11.0 Hz, 1H, 10a-H), 2.40 (s, 2H, 1′-H), 2.36–2.29 (m, 1H, 8-H), 2.29–2.20 (m, 1H, 8-H), 2.01–1.95 (m, 1H, 7-H), 1.71 (td, J=11.5, 2.0 Hz, 1H, 6a-H), 1.58 (t, J=5.5 Hz, 1H, OH), 1.47–1.36 (m, 4H, 7-H, 6β-Me, especially 1.42, s, 6β-Me), 1.11 (s, 3H, 6α-Me). Mass spectrum *m*/*z* (relative intensity) 307 (M^+, 24), 289 (8), 276 (100), 208 (12), 170 (10). Exact mass calculated for $C_{19}H_{21}D_5O_3$, 307.2196; found, 307.2193. The deuterium incorporation on the molecular ion cluster using FI was $^2H_5$: 96.5%, $^2H_4$: 2.1%, $^2H_3$: 0.8%, and $^2H_1$: 0.6%.

4.31. (6a*R*,10a*R*)-6a,7,8,10a-Tetrahydro-1-hydroxy-6,6-dimethyl-3-(3′,3′,3′-$^2H_3$-propyl)-6*H*-dibenzo[*b*,*d*]pyran-9-methanol (21e)

The synthesis was carried out as described for **21b** starting from **20e** (158 mg, 0.47 mmol) and diisobutylaluminum hydride (1.41 mL, 1 M solution in toluene) in anhydrous CH_2Cl_2 (7 mL) and gave 140 mg (97%) of **21e** as a white solid. Mp=135–136 °C; ^1H NMR (500 MHz, $CDCl_3$+CD_3COCD_3) δ 6.71 (m as d, J=1.5 Hz, 1H, 10-H), 6.25 (d, J=1.6 Hz, 1H, 4-H), 6.17 (d, J=1.6 Hz, 1H, 2-H), 5.91 (br s, 1H, OH), 4.03 (br s, 2H, 11-H), 3.26 (br d, J=11.2 Hz, 1H, 10a-H), 2.46–2.37 (m as td, J=7.8, 2.4 Hz, 2H, 1′-H), 2.36–2.29 (m, 1H, 8-H), 2.29–2.20 (m, 1H, 8-H), 2.01–1.95 (m, 1H, 7-H), 1.71 (td, J=11.7, 1.9 Hz, 1H, 6a-H), 1.56 (t, J=7.5 Hz, 2H, 2′-H), 1.51 (br s, 1H, OH), 1.47–1.36 (m, 4H, 7-H, 6β-Me, especially 1.42, s, 6β-Me), 1.11 (s, 3H, 6α-Me). Mass spectrum *m*/*z* (relative intensity) 305 (M^+, 26), 287 (10), 274 (100), 206 (13), 168 (11). Exact mass calculated for $C_{19}H_{23}D_3O_3$, 305.2070; found, 305.2069. The deuterium incorporation on the molecular ion cluster using FI was $^2H_3$: 97.1%, $^2H_2$: 2.2%, and $^2H_1$: 0.7%.

4.32. Single-crystal X-ray diffraction analysis of 15c

$C_{20}H_{28}O_3$, FW=316.42, orthorhombic, $P2_12_12_1$, a=12.4442(2) Å, b=13.8118(2) Å, c=20.9625(3) Å, α=90°, β=90°, γ=90°, V=3602.97(9) Å^3, Z=8, ρ_{calc}=1.167 Mg/mm^3, μ=0.606 mm^{-1}, F(000)=1376, R_1=0.0883 for 5398 observed ($I>2\sigma I$) reflections and 0.0909 for all 5758 reflections, goodness-of-fit=1.064, 412 parameters.

A clear colorless crystal of dimensions 0.30×0.24×0.17 mm^2 was mounted on glass fiber using a small amount of Cargille immersion oil. Data were collected on a three-circle platform diffractometer equipped with a SMART 6000 CCD detector. The crystals were irradiated using a rotating anode Cu Kα source (λ=1.54178) with incident beam Göbel mirrors. A Bruker LT2 low temperature device was used to keep the crystals at a constant −40 °C during data collection.

Data collection was performed and the unit cell was initially refined using *SMART* [v5.625].[53] Data reduction was performed using *SAINT* [v6.36A][54] and *XPREP* [v6.12].[55] Corrections were applied for Lorentz, polarization, and absorption effects using *SADABS* [v2.03].[56] The structure was solved and refined with the aid of the programs in the *SHELXTL-plus* [v6.14] system of programs.[57] The full-matrix least-squares refinement on F^2 included atomic coordinates and anisotropic thermal parameters for ordered non-H atoms. The carbon atoms of the disordered side chain were refined with isotropic thermal parameters. The side chain was disordered over two positions with a population ratio of approximately 60:40. The H atoms were included using a riding model.

The absolute configuration was known due to an unchanging chiral center in the synthetic procedure. This was supported by anomalous dispersion effects in diffraction measurements on the crystal, with a resulting Flack parameter of 0.0(3).[58] CCDC 618020 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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