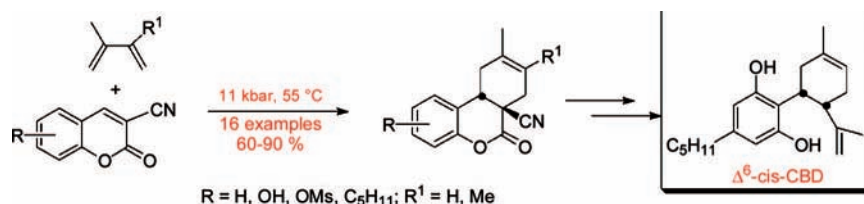# High Pressure Diels−Alder Approach to Hydroxy-Substituted 6a-Cyano-tetrahydro-6H-benzo[c]chromen-6-ones: A Route to Δ⁶-*Cis*-Cannabidiol

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Diels−Alder cycloaddition reactions of 3-cyanocoumarin, hydroxy-substituted 3-cyanocoumarins and mesyl-substituted 3-cyano-coumarins with methyl-1,3-butadienes carried out under high pressure (11 kbar) are reported. Activation by high pressure allows these reactions to proceed satisfactorily under mild conditions to produce 6a-cyano-hydroxy- and 6a-cyano-mesyl-tetrahydro-6H-benzo[c]chromen-6-ones in moderate to excellent yield. The synthesis of *cis*-1-hydroxy-9-methyl-3-pentyl-6a,7,10,10a-tetrahydro-benzo[c]chromen-6-one as precursor of Δ⁶-3,4-*cis*-cannabidiol (Δ⁶-*cis*-CBD) and Δ⁸-*cis*-tetrahydrocannabinol (Δ⁸-*cis*-THC) is outlined.

Introduction

Compounds based on a tetrahydrobenzo[c]chromene skeleton are of great interest in the chemical community and are included in the set of "privileged structures" due to their high incidence in natural biologically active products and as precursors of important molecules (e.g., functionalized biphenyls, cannabinoid compounds).[1] Recently, we focused on the development of new environmentally friendly synthetic routes to obtain target molecules that incorporate the chromane subunit by using the Diels−Alder cycloaddition of 1,3-butadienes to various 3-substituted coumarins.[2] Although the Diels−Alder reaction of 3-substituted coumarins with 1,3-butadienes permits the preparation of interesting synthetic targets, due to the low reactivity of coumarin double bond, these reactions have been scarcely successful. For example, 3-alkoxycarbonylcoumarins react at room temperature in good yield only if a large amount of diene (44 equiv) is used in combination with an excess (1.2 equiv) of

ZnCl₂ as catalyst.[3] In contrast, we have shown that HfCl₄·2THF is an efficient catalyst for Diels−Alder cycloadditions of 3-ethoxycarbonylcoumarins with 1,3-butadienes; the corresponding cycloadducts can be prepared in satisfactory yields under solvent-free conditions (SolFC) at 30−50 °C.[2c] Furthermore, we have reported that 3-nitrocoumarins react with isoprene and 2,3-dimethyl-1,3-butadiene in water or under SolFC in good yields, while the 6- and 7-hydroxy-substituted 3-nitrocoumarins are deactivated by the hydroxy substituent and react only under harsh conditions with moderate yields.[2a] These results highlight the need to find a protocol that allows the cycloaddition reactions of coumarins that have electron-donating groups in the 5−8-positions to be performed under mild conditions. This would provide a competitive, environmentally safe route to the benzo[c]chromene skeleton.

Recently, we reported the 9 kbar pressure (30−70 °C) Diels−Alder reactions of coumarins substituted at C-3 position with phenylsolfonyl-, carboxy-, ethoxycarbonyl-, nitro-, tiofenyl-, and -pyridyl-groups. The corresponding tetrahydro-6H-benzo[c]chromen-6-ones were prepared in excellent yields. When carried out at atmospheric pressure, the reaction yields and selectivities were greatly reduced.[2d]

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SCHEME 1. Diels-Alder Reactions between 3-Cyanocoumarins 1 and 1,3-Butadienes 2

1	a	b	c	d	e	f	g	h	2	x	y
R	H	5-OH	6-OH	7-OH	8-OH	6-OMs	7-OMs	5-OH, 7-C$_5$H$_{11}$	R^1	Me	H
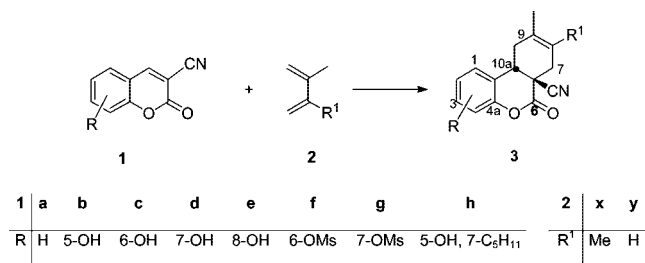
SCHEME 2. Proposed Synthesis of Tetrahydro-6H-benzo[c]chromen-6-ones 4 and 5 and Cannabinoids 6 and 7

	ax	bx	cx	ex	ay	hy
R	H	1-OH	2-OH	4-OH	H	1-OH, 3-C$_5$H$_{11}$
R^1	Me	Me	Me	Me	H	H
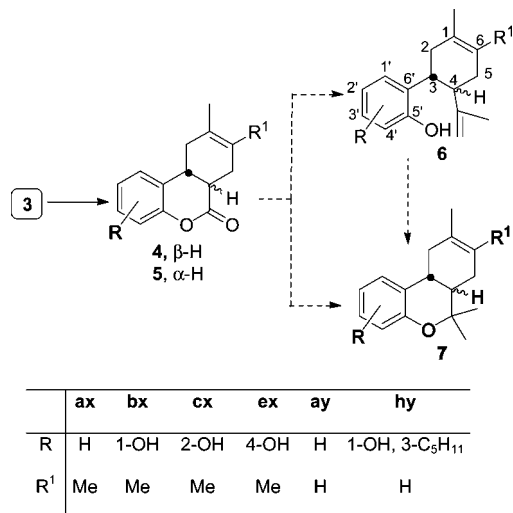
These results have proven that increased pressure promotes efficiently the Diels−Alder cycloadditions of 3-substituted-coumarins under milder condition with no need for a metallic catalyst and/or high temperatures, thus promoting this technology as a valuable tool in eco-friendly processes.[2d,4]

Thus, in continuation of our research directed toward the synthesis of compounds that incorporate the chromene subunit, herein we report (i) the synthesis of 6a-cyano-tetrahydro-6H-benzo[c]chromen-6-ones 3 based on the Diels−Alder cycload-dition under high pressure of 3-cyano-coumarins 1 and 1,3-butadienes 2 (Scheme 1) and (ii) the conversion of selected cycloadducts 3 into their corresponding tetrahydro-6H-benzo-[c]chromen-6-ones 4 and 5, under aqueous conditions. These products are precursors of important molecules, such as iso-propenyl-substituted tetrahydrobiaryl templates 6 and 6,6-dimethyl-tetrahydro-6H-benzo[c]chromene derivatives 7 (Scheme 2).

Specifically, we have applied this approach to the synthesis of *cis*-tetrahydro-6H-benzo[c]chromen-6-one 4hy as precursor

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TABLE 1. Diels−Alder Reactions of Coumarin (1a) with 2,3-Dimethyl-1,3-butadiene (2x) and Isoprene (2y) under Atmospheric and 11 kbar Pressure Conditions

entry	diene^a	medium^b	P (kbar)	T (°C)	t (h)	product	yield (%)^c
1	2x	PhMe	Atm	110	48	3ax	43^d
2	2x^e	SolFC/HfCl$_4$·2THF^e	Atm	55	72	3ax	55^d
3	2x	H$_2$O	Atm	150	3	4ax/5ax^{f,g}	65
4	2x	CH$_2$Cl$_2$	11	55	16	3ax	90
5	2x	MeCN	11	55	16	3ax	85
6	2x	Me$_2$CO	11	55	16	3ax	80
7	2x	EtOAc	11	55	36	3ax	50^d
8	2x	EtOH	11	55	36	3ax	20^d
9	2y	PhMe	Atm	110	48	3ay	38^d
10	2y^e	SolFC/HfCl$_4$·2THF^e	Atm	55	72	3ay	45^d
11	2y	H$_2$O	Atm	150	3	4ay/5ay^{f,h}	60
12	2y	CH$_2$Cl$_2$	11	55	16	3ay	85
13	2x	MeCN	11	55	16	3ay	80
14	2y	Me$_2$CO	11	55	16	3ay	77

^{a} Four equivalents of 1,3-diene were used. ^{b} Concn of coumarin 1a = 0.1 M. ^{c} Yield of isolated product. ^{d} Conversion. ^{e} Ten equivalents of 1,3-diene and 25 mol % of catalyst were used. ^{f} Diastereomeric ratio was determined by GC and/or ^{1}H NMR analyses. ^{g} Diastereomeric ratio 4ax/5ax = 1:1.5. ^{h} Diastereomeric ratio 4ay/5ay = 1:1.4.

SCHEME 3
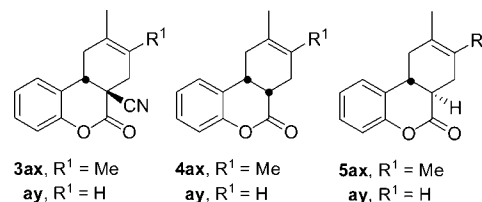
for the synthesis of Δ^6-3,4-*cis*-cannabidiol (Δ^6-*cis*-CBD) 6hy (R = 1′-OH, 3′-C$_5$H$_{11}$; R^1 = H), and Δ^8-*cis*-tetrahydrocannabinol (Δ^8-*cis*-THC) 7hy (R = 1-OH, 3-C$_5$H$_{11}$; R^1 = H)[5] (Scheme 2).

Results and Discussion

Diels−Alder Reactions of 3-Cyanocoumarins 1 with 1,3-Butadienes 2. The Diels−Alder cycloadditions of 3-cy-anocoumarin (1a) with dienes 2 were initially investigated under both atmospheric and high pressure. The results of this study are summarized in Table 1.

Preliminary experiments showed that there was no reaction between 1a and dienes 2 under atmospheric pressure, at low temperature (55 °C) and for long period of time (72 h), neither when toluene, methylene chloride or water, was used as solvent, nor under SolFC. A moderate conversion of 1a to 3ax and 3ay (55%, 45%) was obtained under SolFC at ambient pressure and 55 °C, by using 0.25 molar equivs of HfCl$_4$·2THF (Table 1, entries 2 and 10), or heating for 48 h 1a with dienes 2 in toluene at 110 °C[6] (Table 1, entries 1 and 9). However, under aqueous conditions and an increase of reaction temperature from 55 to 150 °C the reactions of 1a with 2x and 2y gave better isolated yields (65 and 60%, respectively) (Table 1, entries 3 and 11). However, instead of the expected cycloadducts 3ax and 3ay, under the given reaction conditions a mixture of 4ax/5ax[2d] or 4ay/5ay[2d] in ratios of 1:1.5 and 1:1.4, respectively were obtained (Scheme 3).

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TABLE 2. Diels−Alder Reactions of Coumarins (1b−g) with 2,3-Dimethyl-1,3-butadiene (2x) and Isoprene (2y) under 11 kbar Pressure at 55 °C

entry	coumarin[a]	diene[b]	medium	t (h)	product	yield (%)[c]
1	1b	2x	CH₂Cl₂	36	3bx	25[d]
2	1b	2x	Me₂CO	36	3bx	60
3	1b	2x	MeCN	48	3bx	65
4	1b	2y	CH₂Cl₂	48	3by	30[d]
5	1b	2y	Me₂CO	36	3by	60
6	1b	2y	MeCN	48	3by	65
7	1c	2x	Me₂CO	48	3cx	30
8	1c	2y	Me₂CO	60	3cy	10[d]
9	1d	2x	MeCN	48	3dx	12[d]
10	1d	2y	Me₂CO	36	3dy	5[d]
11	1e	2x	Me₂CO	15	3ex	75
12	1e	2y	Me₂CO	15	3ey	65
13	1f	2x	MeCN	20	3fx	75
14	1f	2y	Me₂CO	24	3fy	70
15	1g	2x	MeCN	20	3gx	76
16	1g	2y	Me₂CO	24	3gy	60

[a] Concn of coumarins 1b−g = 0.1 M. [b] Four equivalents of 1,3-diene were used. [c] Yields of isolated cycloadducts. [d] Conversion determined by ¹H NMR of crude reaction mixture.
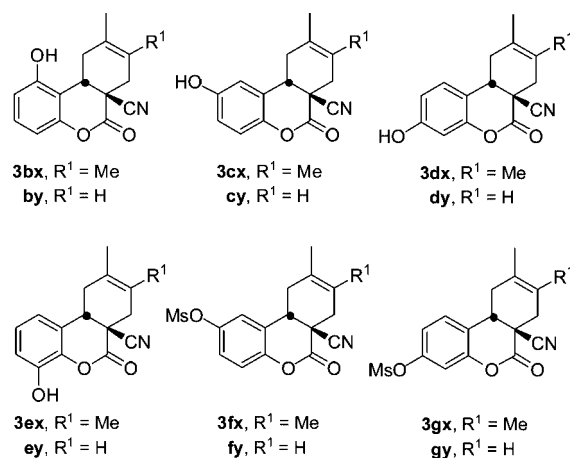
The low yields obtained under harsh reaction conditions (high temperature, long reaction time) and the need to have a metal catalyst in order for the reactions to occur at atmospheric pressure, makes the procedure unattractive. Thus, considering the powerful pressure-induced acceleration of the Diels−Alder reaction,[4] we studied the cycloadditions of coumarin 1a with dienes 2 under high pressure.

When a mixture of coumarin 1a and 2,3-dimethyl-1,3-butadiene (2x) in methylene chloride was compressed to 11 kbar for 16 h at 55 °C, an isolated yield of 90% of 3ax was obtained (Table 1, entry 4). Similarly, isoprene (2y) under identical conditions gave 3ay in high yield (85%) (Table 1, entry 12). The effect of pressure on the reactions of 1a with 2 was also explored in other organic solvents. The use of acetonitrile or acetone led to cycloadducts 3ax and 3ay (Table 1, entries 5, 6, 13, and 14) in yields that were slightly lower than those obtained with methylene chloride (Table 1, entries 4 and 12). When ethyl acetate or ethanol were used the conversions to adduct 3ax were very low (Table 1, entries 7 and 8).

The study was then extended to the hydroxy-substituted-3-cyanocoumarins 1b−e to determine the scope of the reaction (Table 2).

The electron-donating hydroxy group in positions 5−8 of coumarins 1b-e lowered the dienophilicity of coumarins 1b-e toward dienes 2 and reduced their solubility in methylene chloride. Thus, optimized reaction conditions for the reactions of 1a only gave low yields of the corresponding adducts when applied to the reactions of coumarin 1b with dienes 2 (Table 2, entries 1 and 4). When acetone was used as solvent, the cycloadditions of 1b and 1e with 2x occurred under homogeneous condition and gave the corresponding cycloadducts 3bx and 3ex (Scheme 4) in satisfactory yields (60 and 75%, respectively) (Table 2, entries 2 and 11). In the case of isoprene (2y), the cycloadditions with 1b and 1e in acetone were always totally regioselective and produced adducts 3by and 3ey in 60 and 65% yields, respectively (Table 2, entries 5 and 12). The reaction of 1b with 2x and 2y in acetonitrile gave 65% yields (Table 2, entries 3 and 6).

Under homogeneous conditions reactions between coumarins 1c and 1d with both dienes 2 gave low conversions (Table 2, entries 7−10). This result is due to the strong deactivation of

SCHEME 4

3bx, R¹ = Me
by, R¹ = H

3cx, R¹ = Me
cy, R¹ = H

3dx, R¹ = Me
dy, R¹ = H

3ex, R¹ = Me
ey, R¹ = H

3fx, R¹ = Me
fy, R¹ = H

3gx, R¹ = Me
gy, R¹ = H

these substrates by the hydroxy group in the 6- and 7-positions, respectively.

In view of these unsatisfactory results, we converted coumarins 1c and 1d to the corresponding methanesulfonic acid 3-cyano-2-oxo-2H-chromen-6-yl and 7-yl esters 1f and 1g following the usual procedure.[7] These dienophiles were then submitted to Diels−Alder reaction with dienes 2x, y.

The electron-withdrawing capacity of the mesyl group allowed the Diels−Alder reaction of 1f and 1g with 2x to occur with improved yields (75 and 76%, respectively) (Table 2, entries 13 and 15) when performed in acetonitrile solution.[8] With diene 2y (Table 2, entries 14 and 16), the 11 kbar pressure cycloadditions in acetone solution were totally regioselective, producing cycloadducts 3fy and 3gy in 70 and 60% yield, respectively (Scheme 4).

Application to the Synthesis of Cannabinoids. Cannabinoids are a well-known group of about 60 structurally related compounds, that have been isolated from Indian hemp (*Cannabis sativa var. indica*). These compounds, along with their non-natural analogues, have been gaining the attention of synthetic and medicinal chemists because of their important bioactivities and the effect that structural modifications of their skeleton can play on their biological role.[9] In the past decade, the need for further studies has created an increased demand for analogues and metabolites.[10]

To demonstrate the practical utility of our Diels−Alder approach to 6a-cyano-tetrahydro-benzo[c]chromenones 3 in the synthesis of cannabinoids, we first studied the conversion of cycloadducts 3bx, 3cx and 3ex into the corresponding hydroxy-

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(8) The same reactions occur in 70% yield when performed in acetone solution.

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TABLE 3. Diels−Alder Reactions of Coumarin (1h) with 2,3-Dimethyl-1,3-butadiene (2x) and Isoprene (2y) under Atmospheric and 11 kbar Pressure Conditions
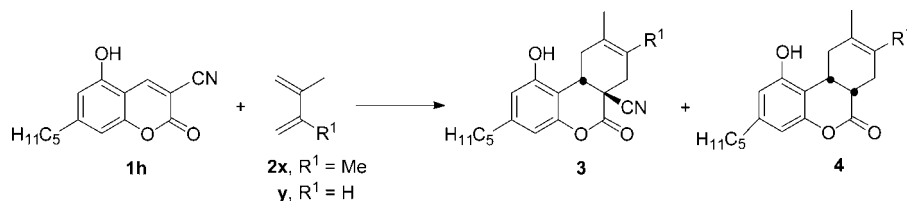
entry	diene (eq.)	medium[a]	P (kbar)	T (°C)	t (h)	product	yield (%)[b]
1	2x (4)	MeCN	11	55	20	3hx	70
2	2x (4)	CH$_2$Cl$_2$	11	55	16	3hx	68
3	2y (3)	H$_2$O	Atm.	150	2	3hy	30
4	2y (3)	H$_2$O	Atm.	150	6	4hy	25
5	2y (7)	SolFC	Atm	150	2	3hy	31
6	2y (7)	SolFC	Atm	150	5	4hy	22
7	2y (4)	MeCN	11	55	24	3hy	80
8	2y (4)	CH$_2$Cl$_2$	11	55	24	3hy	60

[a] Concn of coumarin 1h = 0.1 M;. [b] Yield of isolated cycloadduct.

SCHEME 5. Synthesis of Hydroxy-substituted-tetrahydro-benzo[c]chromenones 4 and 5
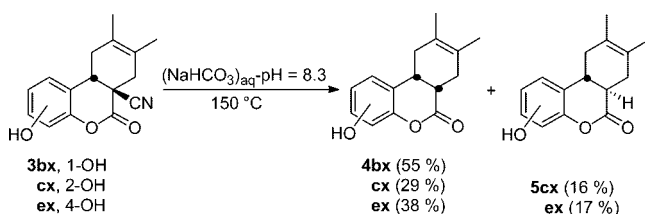
benzo[c]chromenones 4 and 5 (Scheme 5). Heating cycloadduct 3bx in an aqueous solution of NaHCO$_3$ at 150 °C for 6 h selectively gave cis-tetrahydrobenzo[c]chromenone 4bx in 55% yield (Scheme 5). Similar to the results obtained in the Diels−Alder reactions of 3-cyanocoumarin 1a in water (Table 1, entries 3 and 11), adducts 3cx and 3ex led to a mixture of chromenones 4cx/5cx and 4ex/5ex in ratios of 1.8:1 and 2.2:1, respectively (Scheme 5).

We then explored the cycloadditions of 5-hydroxy-7-pentyl-3-cyanocoumarin (1h) with dienes 2x,y to exploit our Diels−Alder approach to the synthesis of cis-tetrahydro-6H-benzo[c]chromen-6-one 4hy, as precursor[5] for the synthesis of cannabinoids Δ^6-cis-CBD 6hy and Δ^8-cis-THC 7hy.

The cycloaddition of 1h with 2x in acetonitrile or methylene chloride solutions occurred in good yields (70 and 68%, respectively) under 11 kbar pressure at 55 °C (Table 3, entries 1 and 2).

The Diels−Alder cycloaddition between 1h and isoprene (2y) was then studied in water and under SolFC at atmospheric pressure and in organic solvent under high pressure. In aqueous conditions, the cycloaddition of 1h with 2y at 150 °C for 2 h (Table 3, entry 3) gave a low yield (30%) affording the cycloadduct 3hy. When the reaction time was increased to 6 h chromenone 4hy was obtained in 25% yield (Table 3, entry 4). Similar results were obtained when this reaction was carried out under SolFC at 150 °C for 2 and 5 h, respectively (Table 3, entries 5 and 6). Previously, lactone 4hy was prepared from isoprene (2y) and 3-carboxy-5-hydrox-7-pentylcoumarin in xylene solution by Diels−Alder cycloaddition accompanied by a decarboxylation reaction at 180 °C for 18 h.[5] When the reaction between coumarin 1h and isoprene (2y) was carried out in acetonitrile, under 11 kbar pressure, cycloadduct 3hy was regioselectively produced in good yield (80%) under mild reaction temperature (55 °C) (Table 3, entry 7).

Finally, cycloadduct 3hy in aqueous solution of NaHCO$_3$ was heated at 150 °C for 2 h and produced the expected chromenone 4hy in 60% yield.[5] Methylation of 4hy and subsequent dehydratation to Δ^6-cis-CBD 6hy and/or cyclization to (Δ^8-cis-THC) 7hy (Scheme 6) have been reported in the literature.[5]

**Structural Analysis.** All of the 6a,7,10,10a-tetrahydro-6H-benzo[c]chromen-6-ones 3, 4 and 5 prepared in this work are new compounds except 3ay,[6] 4ax,[2d] 5ax,[2d] 4ay,[2d] 5ay[2d] and 4hy.[5] However, for compounds 3ay and 4hy incomplete ^{1}H NMR characterization has been reported. The structure and stereochemistry of the products were assigned by analyzing the ^{1}H and ^{13}C NMR spectra. The structures of all the new 6a-cyano-benzo[c]chromenones 3 have been assigned based on the comparison of their NMR data with those of similar 6a-substituted-benzo[c]chromen-6-ones.[2d]

The assignment of cis/trans stereochemistry at the C(6a)-C(10a) ring junction of compounds 4bx,cx,ex,hy and 5cx,ex was based on the relevant $J_{H,H}$ coupling constant values. The 10.9−13.4 Hz and the 5.4−5.8 Hz measured for $^3J_{10a,10\alpha}$ and $^3J_{10a,10\beta}$ respectively, revealed a pseudoaxial orientation of H(10a) with respect to the cyclohexene ring in all the compounds. Thus, in accord with the $^3J_{6a,10a}$ values previously reported[2d] for 4ax,ay and 5ax,ay, the 5.5−5.8 Hz coupling constant values between H(10a) and H(6a) for 4bx,cx,ex,hy indicate their cis-relationship, whereas the 10.9 and 10.8 H$_z$ coupling constant values between H(10a) and H(6a) for 5cx and 5ex respectively, indicate their trans stereochemistry (Table 4).

Conclusions

Even though hydroxy-substituted 3-cyano-coumarins 1b-e,h, behave as poor dienophiles in [4 + 2] cycloaddition, under 11 kbar of pressure they react with 1,3-dienes 2x,y under milder reaction temperature and without any metal catalyst to produce 6a-cyano-hydroxy-substituted benzo[c]chromenones 3 in good-to-high yields. This protocol, is the first high-yielding synthetic approach to this important class of heterocyclic compounds.

This approach has been applied to the synthesis hydroxy-substituted-tetrahydro-benzo[c]chromenones 4 and 5, including cis-1-hydroxy-9-methyl-3-pentyl-6a,7,10,10a-tetrahydro-benzo[c]chromen-6-one(4hy), precursor of cannabinoids Δ^6-cis-CBD 6hy and Δ^8-cis-THC 7hy, by performing a decyanation reaction of the cycloadducts 3 in aqueous solution of NaHCO$_3$.

SCHEME 6.   Synthesis of Δ⁶-*cis*-CBD 6hy and Δ⁸-*cis*-THC 7hy
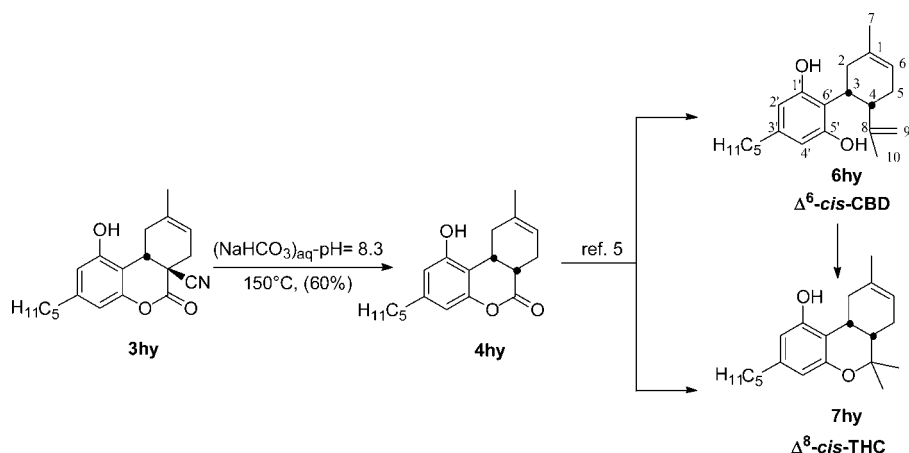
TABLE 4. $^3J_{H,H}$ Coupling Constant Values (Hz) of H(10a) of Compounds 4 and 5

compound	$^3J_{6a,10a}$	$^3J_{10a,10\alpha}$	$^3J_{10a,10\beta}$
4ax[2d]	5.5	11.0	5.5
4bx	5.6	11.3	5.6
4cx	5.5	10.9	5.5
4ex	5.5	10.9	5.5
4ay[2d]	5.0	10.9	5.9
4hy	5.8	11.5	5.8
5ax[2d]	10.6	13.0	5.4
5ay[2d]	11.8	12.3	5.6
5cx	10.9	13.4	5.6
5ex	10.8	11.8	5.5

Considering that 3-cyano-hydroxy-substituted-coumarins **1** can be readily prepared by Knoevenagel condensation between salicylic aldehydes and malonitrile,[11] by using water as reaction medium, our proposed strategy to hydroxy-tetrahydro-benzo[c]-chromen-6-ones nucleous **3**, **4** and **5** is also a new environmentally friendly synthetic route to non natural cannabinoids **6** and **7**.

Experimental Section

General Procedure for the Diels−Alder Reaction of 3-Cyanocoumarins 1a−h with Dienes 2x,y. The cycloadditions of **1** with **2** were accomplished (A) in water, toluene and SolFC at normal pressure and (B) under 11 kbar pressure conditions. Details are listed in Tables 1−3.

Conditions (A). Diene **2** (3 or 4 equiv) and few crystals of hydroquinone (1−2 mg) were added to a metal reactor containing coumarin **1** (0.3 mmol) and 3 mL of solvent (0.1 M). In the case of experiments without solvent (SolFC), diene **2** (7 or 10 equiv) and 1−2 mg of hydroquinone were added directly to coumarin **1**. The reactor was sealed and poured into an oil bath under magnetic stirring at the indicated reaction temperature and time. After cooling, the mixture was evaporated under vacuo and the residue was purified by column chromatography on silica gel followed by recrystallization.

Conditions (B). A solution of compound **1** (1.5 mmol), diene **2** (4 molar equiv) and a few crystals of hydroquinone in 10 mL of the appropriate solvent were placed in a 15 mL Teflon vial that was then filled with the solvent. The vial was closed and kept at 11 kbar at the indicated temperature for the appropriate time. After depressurizing, the solvent was removed in vacuo. The crude

mixture was purified by column chromatography on silica gel followed by recrystallization, to give cycloadducts **3**.

3ax. White solid, mp 84−85 °C (*n*-exane/chloroform); IR (KBr) ν: 2241 (CN), 1782 (C=O) cm⁻¹; ¹H NMR (200 MHz, CDCl₃) δ 1.65 (s, 6H, 2 CH₃), 2.21 (dd broad, 1H, J = 17.6, 8.6 Hz, H-10α), 2.48 (dd broad, 1H, J = 17.6, 6.0 Hz, H-10β), 2.55 (d broad, 1H, J = 17.3 Hz, H-7α), 2.85 (d broad, 1H, J = 17.3 Hz, H-7β), 3.45 (dd, 1H, J = 8.6, 6.0 Hz, H-10a), 7.10−7.39 (m, 4H, H-1, H-2, H-3, H-4); ¹³C NMR (50.3 MHz, CDCl₃) δ 18.1, 18.5 (8-Me, 9-Me), 32.9, 34.4 (C-7, C-10), 37.6 (C-10a), 41.9 (C-6a), 116.8 (C-4), 117.3 (CN), 121.1, 123.1, 123.9 (C-8, C-9, C-10b), 125.4, 126.8 (C-2, C-3), 129.2 (C-1), 150.0 (C-4a), 162.4 (C-6); MS, *m/e* (relative intensity) 253 (M⁺, 45), 121 (15), 120 (100), 115 (15), 82 (83), 77 (17), 67 (70). Anal. Calcd for C₁₆H₁₅NO₂: C, 75.87; H, 5.97; N, 5.53. Found: C, 75.83; H, 5. 99; N, 5.51.

3ay. White solid, mp 97−98 °C (*n*-exane/ethyl acetate) (lit.[7] mp 93−95 °C); IR (KBr) ν: 2241 (CN), 1787 (C=O) cm⁻¹; ¹H NMR (200 MHz, CDCl₃) δ 1.66 (s, 3H, CH₃), 2.17 (dd broad, 1H, J = 18.3, 8.0 Hz, H-10α), 2.36−2.64 (m, 2H, H-7α, H-10β), 2.85 (dddd, 1H, J = 17.6, 7.6, 3.7, 1.9 Hz, H-7β), 3.47 (dd, 1H, J = 8.0, 6.0 Hz, H-10a), 5.30 (s broad, 1H, H-8), 7.00−7.40 (m, 4H, H-1, H-2, H-3, H-4); ¹³C NMR (50.3 MHz, CDCl₃) δ 23.0 (9-Me), 29.1 (C-10), 31.1 (C-7), 37.3 (C-10a), 41.0 (C-6a), 115.8, 116.9 (C-4, C-8), 117.3 (CN), 123.6 (C-10b), 125.5, 126.7 (C-2, C-3), 129.4 (C-1), 131.4 (C-9), 150.1 (C-4a), 162.6 (C-6); MS, *m/e* (relative intensity) 239 (M⁺, 97), 210 (24), 172 (16), 120 (100), 77 (13), 68 (75). Anal. Calcd for C₁₅H₁₃NO₂: C, 75.30; H, 5.48; N, 5.85. Found: C, 75.39; H, 5. 45; N, 5.83.

3bx. White solid, mp 173−174 °C (n-exane/ethyl acetate); IR (CHCl₃) ν: 2242 (CN), 1780 (C=O) cm⁻¹; ¹H NMR [400 MHz, (CD₃)₂CO] δ 1.62 (s, 3H, CH₃), 1.72 (s, 3H, CH₃), 1.84 (m broad, 1H, H-10α), 2.41 (dd, 1H, J = 18.2, 6.2 Hz, H-10β), 2.80 (d broad, 1H, J = 17.6 Hz, H-7α), 3.05 (d broad, 1H, J = 17.6 Hz, H-7β), 3.85 (dd, 1H, J = 11.4, 6.2 Hz, H-10a), 6.69 (dd, 1H, J = 8.2, 0.9 Hz, H-2), 6.83 (d, 1H, J = 8.2 Hz, H-4), 7.22 (t, 1H, J = 8.2 Hz, H-3), 9.26 (s broad, 1H, OH); ¹³C NMR [100.6 MHz, (CD₃)₂CO] δ 17.5, 17.6 (8-Me, 9-Me), 33.0 (C-10a), 33.3, 35.1 (C-7, C-10), 41.1 (C-6a), 107.7, 112.01 (C-2, C-4), 113.1 (C-10b), 117.5 (CN), 121.4, 123.0 (C-8, C-9), 129.3 (C-3), 151.4 (C-4a), 154.5 (C-1), 162.1 (C-6); MS, *m/e* (relative intensity) 269 (M⁺, 79), 226 (12), 188 (15), 159 (10), 136 (873), 82 (100), 67 (54). Anal. Calcd for C₁₆H₁₅NO₃: C, 71.36; H, 5.61; N, 5.20. Found: C, 70.83; H, 5. 99; N, 5.31.

3by. Oil, IR (KBr) ν: 1776 (C=O) cm⁻¹; ¹H NMR [400 MHz, (CD₃)₂CO] δ 1.67 (s, 3H, CH₃), 1.83 (m broad, 1H, H-10α), 2.45 (dd, 1H, J = 17.8, 5.8 Hz, H-10β), 2.80 (d broad, 1H, J = 18.4 Hz, H-7β), 3.19 (d broad, 1H, J = 18.4 Hz, H-7β), 3.90 (dd, 1H, J = 11.5, 6.2 Hz, H-10a), 5.45 (s broad, 1H, H-8),), 6.69 (d, 1H, J = 9.2 Hz, H-2), 6.84 (d, 1H, J = 9.2 Hz, H-4), 7.24 (t, 1H, J = 8.2 Hz, H-3),), 9.26 (s broad, 1H, OH); ¹³C NMR [100.6 MHz,

(11) Brufola, G.; Fringuelli, F.; Piermatti, O.; Pizzo, F. *Heterocycles* **1996**, *43*, 1257–1266.

(CD$_3$)$_2$CO] δ 22.9 (9-Me), 30.7 (C-10), 32.7 (C-7), 33.8 (C-10a), 41.2 (C-6a), 108.7, 113.0 (C-2, C-4), 114.2 (C-10b), 117.2 (C-8), 118.6 (CN), 130.3 (C-3), 132.2 (C-9), 152.3 (C-4a), 155.4 (C-1), 162.6 (C-6); MS, *m/e* (relative intensity) 255 (M$^+$, 100), 226 (10), 212 (10), 187 (55), 159 (20), 136 (46), 68 (77). Anal. Calcd for C$_{15}$H$_{13}$NO$_3$: C, 70.58; H, 5.13; N, 5.49. Found: C, 70.39; H, 5. 45; N, 5.63.

3cx. White solid, mp 174−175 °C (*n*-exane/ethyl acetate); IR (CHCl$_3$) ν: 2242 (CN), 1772 (C=O) cm^{-1}; ^{1}H NMR [400 MHz, (CD$_3$)$_2$CO] δ 1.65 (s, 3H, CH$_3$), 1.68 (s, 3H, CH$_3$), 2.23 (dd broad, 1H, *J* = 18.7, 7.9 H-10α), 2.53 (dd broad, 1H, *J* = 18.7, 6.1 Hz, H-10β), 2.56 (d, 1H, *J* = 16.6 Hz, H-7α), 2.74 (d, 1H, *J* = 16.6 Hz, H-7β), 3.67 (dd, 1H, *J* = 7.9, 6.1 Hz, H-10a), 6.85 (dd, 1H, *J* = 8.6, 2.8 Hz, H-3), 6.88 (d, 1H, *J* = 2.8 Hz, H-1), 7.00 (d, 1H, *J* = 8.6 Hz, H-3), 8.62 (s broad, 1H, OH); ^{13}C NMR [100.6 MHz, (CD$_3$)$_2$CO] δ 17.5, 17.9 (8-Me, 9-Me), 32.5, 34.4 (C-7, C-10), 37.2 (C-10a), 42.2 (C-6a), 113.5 (C-3), 115.5 (C-1), 117.5 (C-4), 117.7 (CN), 121.2, 1234, 125.6 (C-8, C-9, C-10b), 143.4 (C-4a), 154.7 (C-2), 162.9 (C-6); MS, *m/e* (relative intensity) 269 (M$^+$, 52), 240 (20), 226 (11), 187 (28), 159 (9), 136 (100), 82 (23). Anal. Calcd for C$_{16}$H$_{15}$NO$_3$: C, 71.36; H, 5.61; N, 5.20. Found: C, 70.95; H, 5. 89; N, 5.42.

3ex. White solid, mp 141−142 °C (*n*-exane/ethyl acetate); IR (CHCl$_3$) ν: 2242 (CN), 1778 (C=O) cm^{-1}; ^{1}H NMR [400 MHz, (CD$_3$)$_2$CO] δ 1.65 (s, 3H, CH$_3$), 1.67 (s, 3H, CH$_3$), 2.25 (dd broad, 1H, 18.3, 8.0 Hz, H-10α), 2.52 (dd broad, 1H, *J* = 18.3, 6.1 Hz, H-10β), 2.59 (d, 1H, *J* = 17.3 Hz, H-7α), 2.77 (d, 1H, *J* = 17.3 Hz, H-7β), 3.72 (dd, 1H, *J* = 8.0, 6.1 Hz, H-10a), 6.89 (dd, 1H, *J* = 7.6, 1.5 Hz, H-3), 6.97 (dd, 1H, *J* = 8.2, 1.5 Hz, H-1), 7.08 (t, 1H, *J* = 8.1 Hz, H-2), 8.80 (s broad, 1H, OH); ^{13}C NMR [100.6 MHz, (CD$_3$)$_2$CO] δ 17.5, 17.9 (8-Me, 9-Me), 32.7, 34.4 (C-7, C-10), 37.4 (C-10a) 42.2 (C-6a), 116.8, 117.5 (C-1, C-3), 117.6 (CN), 121.1, 123.5, (C-8, C-9), 125.6 (C-2), 125.7 (C-10b), 138.4 (C-4a), 144.9 (C-4), 162.4 (C-6); MS, *m/e* (relative intensity) 269 (M$^+$, 71), 240 (18), 226 (29), 187 (13), 136 (100), 82 (39), 67 (23). Anal. Calcd for C$_{16}$H$_{15}$NO$_3$: C, 71.36; H, 5.61; N, 5.20. Found: C, 71.73; H, 5. 29; N, 5.15.

3ey. White solid, mp 190−191 °C (*n*-exane/ethyl acetate), IR (CHCl$_3$) ν: 1775 (C=O) cm^{-1}; ^{1}H NMR [400 MHz, (CD$_3$)$_2$CO] δ 1.73 (s, 3H, CH$_3$), 2.30 (dd broad, 1H, *J* = 18.3, 7.4 Hz H-10α), 2.54 (dd broad, 1H, *J* = 18.3, 6.0 Hz, H-10β), 2.62 (d broad, 1H, *J* = 17.6 Hz, H-7β), 2.81 (d broad, 1H, *J* = 18.4 Hz, H-7β), 3.80 (dd, 1H, *J* = 7.4, 6.0 Hz, H-10a), 5.37 (s broad, 1H, H-8),), 6.90 (dd, 1H, *J* = 8.9, 1.5 Hz, H-3), 6.98 (dd, 1H, *J* = 8.2, 1.5 Hz, H-1), 7.09 (t, 1H, *J* = 7.9 Hz, H-2), 8.77 (s broad, 1H, OH); ^{13}C NMR [100.6 MHz, (CD$_3$)$_2$CO] δ 23.2 (9-Me), 30.4, 31.7 (C-7, C-10), 38.0 (C-10a), 42.2 (C-6a), 116.8, 117.7, 118.2 (C-1, C-3, C-8), 118.6 (CN), 126.4 (C-10b), 126.6 (C-2), 132.7 (C-9), 139.1 (C-4a), 145.8 (C-4), 163.2 (C-6); MS, *m/e* (relative intensity) 255 (M$^+$, 100), 226 (35), 212 (32), 187 (39), 159 (15), 136 (84), 68 (21). Anal. Calcd for C$_{15}$H$_{13}$NO$_3$: C, 70.58; H, 5.13; N, 5.49. Found: C, 70.22; H, 5. 11; N, 5.48.

3fx. Pale-yellow solid, mp 112−113 °C (*n*-exane/ethyl acetate); IR (CHCl$_3$) ν: 2244 (CN), 1784 (C=O) cm^{-1}; ^{1}H NMR [400 MHz, (CD$_3$)$_2$CO] δ 1.64(s, 3H, CH$_3$), 1.70 (s, 3H, CH$_3$), 2.38 (dd broad, 1H, *J* = 18.1, 6.7 Hz, H-10α), 2.62 (m, 2H, H-10β, H-7α), 2.70 (d broad, 1H, *J* = 17.3 Hz, H-7β), 3.31 (s, 3H, SCH$_3$), 3.90 (t, 1H, *J* = 6.7 Hz, H-10a), 7.29 (d, 1H, *J* = 8.8 Hz, H-4), 7.42 (dd, 1H, *J* = 8.8, 2.8 Hz, H-3), 7.47 (d, 1H, *J* = 2.8 Hz, H-1); ^{13}C NMR [100.6 MHz, (CD$_3$)$_2$CO] δ 18.3, 18.7 (8-Me, 9-Me), 32.6, 34.9 (C-7, C-10), 37.5 (OSO$_2$CH$_3$), 37.6 (C-10a), 42.9 (C-6a), 118.2 (CN), 119.1 (C-4), 122.0, 124.2, 126.9 (C-8, C-9, C-10b), 122.1 (C-3), 124.1 (C-1), 147.3 (C-4a), 149.9 (C-2), 163.2 (C-6); MS, *m/e* (relative intensity) 347 (M$^+$, 44), 268 (21), 240 (17), 214 (100), 135 (26), 82 (52), 79 (12), 67 (25). Anal. Calcd for C$_{17}$H$_{17}$NO$_5$S: C, 58.78; H, 4.93; N, 4.03; S, 9.23. Found: C, 58.83; H, 5. 09; N, 4.22; S, 9.33.

3fy. Pale-yellow solid, mp 100−101 °C (*n*-exane/ethyl acetate); IR (CHCl$_3$) ν: 2244 (CN), 1782 (C=O) cm^{-1}; ^{1}H NMR [400 MHz,

(CD$_3$)$_2$CO] δ 1.76 (s, 3H, CH$_3$), 2.45 (dd broad, 1H, *J* = 18.0, 6.6 Hz, H-10α), 2.64 (m, 2H, H-10β, H-7α), 2.73 (d broad, 1H,, *J* = 16.5 Hz, H-7β), 3.31 (s, 3H, SCH$_3$), 3.98 (t, 1H, *J* = 6.4 Hz, H-10a), 5.38 (s broad, 1H, H-8), 7.29 (d, 1H, *J* = 8.8 Hz, H-4), 7.42 (dd, 1H, *J* = 8.8, 2.7 Hz, H-3), 7.49 (d, 1H, *J* = 2.7 Hz, H-1); ^{13}C NMR [100.6 MHz, (CD$_3$)$_2$CO] δ 23.2 (9-Me), 29.6, 30.7 (C-7, C-10), 37.3 (OSO$_2$CH$_3$), 37.6 (C-10a), 42.0 (C-6a), 116.7 (C-4), 118.2 (CN), 119.1, 122.1, 124.2 (C-1, C-3, C-8), 126.7, 132.6 (C-9, C-10b), 147.4 (C-4a), 149.9 (C-2), 163.4 (C-6); MS, *m/e* (relative intensity) 333 (M$^+$, 100), 254 (78), 226 (47), 214 (59), 199 (52), 186 (23), 128 (18), 68 (28). Anal. Calcd for C$_{16}$H$_{15}$NO$_5$S: C, 57.65; H, 4.54; N, 4.20; S, 9.62. Found: C, 57.77; H, 4. 65; N, 4.31; S, 9.35.

3gx. Pale-yellow oil; IR (CHCl$_3$) ν: 2244 (CN), 1787 (C=O) cm^{-1}; ^{1}H NMR [400 MHz, (CD$_3$)$_2$CO] δ 1.64 (s, 3H, CH$_3$), 1.70 (s, 3H, CH$_3$), 2.39 (m broad, 1H, H-10α), 2.59 (m, 2H, H-10β, H-7α), 2.72 (d broad, 1H, *J* = 18.3 Hz, H-7β), 3.36 (s, 3H, OSO$_2$CH$_3$), 3.88 (t, 1H, *J* = 6.7 Hz, H-10a), 7.22 (d, 1H, *J* = 2.4 Hz, H-4), 7.26 (dd, 1H, *J* = 8.4, 2.4 Hz, H-2), 7.58 (d, 1H, *J* = 8.4 Hz, H-1); ^{13}C NMR [100.6 MHz, (CD$_3$)$_2$CO] δ 17.4, 17.8 (8-Me, 9-Me), 31.8, 33.9 (C-7, C-10), 36.4 (C-10a), 36.9 (OSO$_2$CH$_3$), 42.1 (C-6a), 111.1 (C-4), 117.3 (CN), 119.1 (C-2), 121.0, 123.3 (C-8, C-9, C-10b), 128.5 (C-1), 149.5 (C-4a), 150.8 (C-3), 162.2 (C-6); MS, *m/e* (relative intensity) 347 (M$^+$, 24), 214 (94), 187 (13), 135 (6), 82 (100), 67 (42). Anal. Calcd for C$_{17}$H$_{17}$NO$_5$S: C, 58.78; H, 4.93; N, 4.03; S, 9.23. Found: C, 59.03; H, 5. 19; N, 4.13; S, 9.15.

3gy. Pale-yellow solid; mp 134−135 °C (*n*-exane/ethyl acetate); IR (CHCl$_3$) ν: 2244 (CN), 1789 (C=O) cm^{-1}; ^{1}H NMR [400 MHz, (CD$_3$)$_2$CO] δ 1.76 (s, 3H, CH$_3$), 2.46 (dd broad, 1H, *J* = 18.3, 6.1 Hz, H-10α), 2.61 (d broad, 2H, *J* = 17.3 Hz, H-10β, H-7α), 2.71 (d broad, 1H, *J* = 15.7 Hz, H-7β), 3.36 (s, 3H, OSO$_2$CH$_3$), 3.97 (t, 1H, *J* = 6.1 Hz, H-10a), 5.38 (s broad, 1H, H-8), 7.23 (d, 1H, *J* = 2.3 Hz, H-4), 7.27 (dd, 1H, *J* = 8.4, 2.3 Hz, H-2), 7.60 (d, 1H, *J* = 8.4 Hz, H-1); ^{13}C NMR [100.6 MHz, (CD$_3$)$_2$CO] δ 22.4 (9-Me), 28.8, 29.9 (C-7, C-10), 36.2 (C-10a), 37.0 (OSO$_2$CH$_3$), 41.4 (C-6a), 111.2 (C-4), 115.8 (C-2), 117.4 (CN), 119.3 (C-8), 123.1 (C-10b), 128.5 (C-1), 131.7 (C-9), 149.7 (C-4a), 151.0 (C-3), 162.4 (C-6); MS, *m/e* (relative intensity) 333 (M$^+$, 59), 265 (26), 214 (59), 187 (64), 68 (100). Anal. Calcd for C$_{16}$H$_{15}$NO$_5$S: C, 57.65; H, 4.54; N, 4.20; S, 9.62. Found: C, 57.77; H, 4. 65; N, 4.31; S, 9.35.

3hx. Oil; IR (KBr) ν: 2260 (CN), 1780 (C=O) cm^{-1}; ^{1}H NMR [200 MHz, (CDCl$_3$] δ 0.89 (s, 3H, CH$_3$), 1.10−1.45 (m, 4H, CH$_2$CH$_2$), 1.45−1.75 (m, 2H CH$_2$), 1.59 (s, 3H, CH$_3$), 1.71 (s, 3H, CH$_3$), 1.86 (dd broad, 1H, *J* = 18.3, 11.4 Hz H-10α), 2.39 (dd, 1H, *J* = 18.3, 6.2 Hz, H-10β), 2.52 (t, 2H, *J* = 7.3 Hz, ArCH$_2$), 2.66 (d broad, 1H, *J* = 17.5 Hz, H-7α), 3.14 (d broad, 1H, *J* = 17.5 Hz, H-7β), 3.72 (dd, 1H, *J* = 11.4, 6.2 Hz, H-10a), 5.75 (s broad, 1H, OH), 6.45 (d, 1H, *J* = 1.3 Hz, H-4), 6.55 (d, 1H, *J* = 1.3 Hz, H-2); ^{13}C NMR [50.3 MHz, CHCl$_3$] δ 13.9 (C-5′), 18.3, 18.6 (8-Me, 9-Me), 22.4 (C-4′), 30.5, 31.4 (C-2′, C-3′), 33.4 (C-10a), 33.8 (C-10), 35.7 (C-1′, C-7), 41.3 (C-6a), 109.2 (C-4), 110.3 (C-10b), 112.2 (C-2), 117.7 (CN), 121.4, 123.4 (C-8, C-9), 145.2 (C-3), 151.2 (C-4a), 152.6 (C-1), 162.5 (C-6); MS, *m/e* (relative intensity) 339 (M$^+$, 39), 338 (31), 258 (20), 206 (26), 201 (56), 82 (100), 77 (9), 67 (33). Anal. Calcd for C$_{21}$H$_{25}$NO$_3$: C, 74.31; H, 7.42; N, 4.13. Found: C, 74.64; H, 7. 99; N, 4.31.

3hy. White solid; mp 139−140 °C (n-exane/ethyl acetate); IR (KBr) ν: 2400 (CN), 1772 (C=O) cm^{-1}; ^{1}H NMR [200 MHz, (CDCl$_3$] δ 0.94 (s, 3H, CH$_3$), 1.10−1.50 (m, 4H, CH$_2$CH$_2$), 1.50−2.00 (m, 3H, CH$_2$, H-10α), 1.66 (s, 3H, CH$_3$), 2.41 (dd broad, 1H, *J* = 18.1, 6.2 Hz, H-10β), 2.54 (t, 2H, *J* = 7.3 Hz, ArCH$_2$), 2.68 (d broad, 1H, *J* = 17.9 Hz, H-7α), 3.29 (d broad, 1H, *J* = 17.9 Hz, H-7β), 3.76 (dd, 1H, *J* = 11.4, 6.2 Hz, H-10a), 5.40 (m, 1H, H-8), 5.64 (s broad, 1H, OH), 6.47 (d, 1H, *J* = 1.3 Hz, H-4), 6.57 (d, 1H, *J* = 1.3 Hz, H-2); ^{13}C NMR (50.3 MHz, CHCl$_3$) δ 13.9 (C-5′), 22.4 (C-4′), 22.8 (9-Me), 30.2, 30.5, 31.4, 32.3 (C-2′, C-3′, C-7, C-10), 33.1 (C-10a), 35.6 (C-1′), 40.4 (C-6a), 109.0 (C-4), 110.2 (C-10b), 112.3 (C-2), 116.0 (C-8), 117.7 (CN), 131.6 (C-

9), 145.2 (C-3), 151.1 (C-4a), 152.8 (C-1), 162.4 (C-6); MS, *m/e* (relative intensity) 325 (M⁺, 38), 269 (27), 257 (23), 201 (100), 173 (6), 150 (8), 77 (10), 68 (37). Anal. Calcd for $C_{20}H_{23}NO_3$: C, 73.82; H, 7.12; N, 4.30. Found: C, 74.04; H, 6. 99; N, 4.31.

General Procedure for the Decyanation Reaction of 3bx,cx, ex,hy. Cycloadduct **3** (0.15 mmol) was added to a 0.05 M aqueous solution of $NaHCO_3$ (3 mL) in a metal reactor and the mixture was heated at 150 °C (6 h for **3bx,cx,ex** and 2 h for **3hy**) under stirring. After cooling to room temperature, the mixture was then transferred into a separatory funnel and extracted with ethyl acetate. The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified by column cromatography (silica gel, 4:1 petroleum ether-ethyl acetate), to give tetrahydro-benzo[c]chromen-6-ones **4** and **5**.

4bx. White solid, mp 208−210 °C (*n*-exane/ethyl acetate); IR (KBr) *ν*: 3270 (OH), 1764 (C=O) cm⁻¹; ¹H NMR (200 MHz, $(CD_3)_2CO$) δ 1.58 (s, 3H, CH_3), 1.67 (s, 3H, CH_3), 1.75 (m, 1H, H-10α), 2.10−2.45 (m, 2H, H-7α, H-10β), 2.66 (d broad, 1H, *J* = 17.8 Hz, H-7β), 3.03 (t broad, 1H, *J* = 5.6 Hz, H-6a), 3.46 (ddd, 1H, *J* = 11.3, 5.6, 5.6 Hz, H-10a), 6.50 (dd, 1H, *J* = 8.1, 1.1 Hz, H-4), 6.68 (dd, 1H, *J* = 8.1, 1.1 Hz, H-2), 7.06 (t, 1H, *J* = 8.1 Hz, H-3), 8.89 (s broad, 1H, OH); ¹³C NMR [50.3 MHz, $(CD_3)_2CO$] δ 18.0, 18.1 (8-Me, 9-Me), 28.7 (C-10a), 30.0 (C-10), 33.6 (C-7), 38.0 (C-6a), 107.6, 110.9 (C-2, C-4), 116.0 (C-10b), 123.0, 123.4 (C-8, C-9), 128.0 (C-3), 146.0 (C-4a), 154.2 (C-1), 169.6 (C-6); MS, *m/e* (relative intensity) 244 (M⁺, 45), 201 (21), 162 (100), 134 (25), 77 (16), 67 (70). Anal. Calcd for $C_{15}H_{16}O_3$: C, 73.75; H, 6.60; N, 5.20. Found: C, 73.80; H, 5. 21.

4cx. White solid, mp 155−156 °C (diethyl ether); IR (KBr) *ν*: 3596 (OH), 1758 (C=O) cm⁻¹; ¹H NMR (200 MHz, CDCl₃) δ 1.58 (s, 3H, CH_3), 1.66 (s, 3H, CH_3), 1.87−2.37 (m, 3H, H-7α, H-10α, H-10β), 2.65 (d broad, 1H, *J* = 17.7 Hz, H-7β), 2.97 (t broad, 1H, *J* = 5.5 Hz, H-6a), 3.04 (ddd, 1H, *J* = 10.9, 5.5, 5.5 Hz, H-10a), 6.50 (s broad, 1H, OH), 6.71 (s broad, 1H, H-1), 6.74 (dd, 1H, *J* = 8.7, 2.8 Hz, H-3), 6.88 (d, 1H, *J* = 8.7 Hz, H-4); ¹³C NMR [50.3 MHz, CDCl₃] δ 18.7, 18.9 (8-Me, 9-Me), 29.9 (C-10), 34.5 (C-6a), 34.9 (C-7), 38.5 (C-10a), 113.6, 114.7, 117.6 (C-1, C-3, C-4), 123.2, 123.6 (C-8, C-9), 129.2 (C-10b), 144.5 (C-4a), 152.6 (C-2), 171.7 (C-6); MS, *m/e* (relative intensity) 244 (M⁺, 36), 216 (12), 162 (100), 134 (30), 94 (7), 77 (10). Anal. Calcd for $C_{15}H_{16}O_3$: C, 73.75; H, 6.60. Found: C, 73.80; H, 6. 55.

5cx. White solid, mp 195−196 °C (diethyl ether); IR (KBr) *ν*: 3596 (OH), 1758 (C=O) cm⁻¹; ¹H NMR [200 MHz, $(CD_3)_2CO$] δ 1.69 (s, 6H, 2 CH_3), 2.00−2.75 (m, 5H, H-7α, H-7β, H-6a, H-10α, H-10β), 2.94 (ddd, 1H, *J* = 13.4, 10.9, 5.6 Hz, H-10a), 6.67−6.87 (m, 3H, H-1, H-3, H-4); ¹³C NMR [50.3 MHz, $(CD_3)_2CO_3$] δ 18.9 (8-Me, 9-Me), 33.3 (C-10), 34.0 (C-6a), 36.6 (C-7), 39.8 (C-10a), 112.9, 115.3, 117.7 (C-1, C-3, C-4), 124.4, 125.0 (C-8, C-9), 128.8 (C-10b), 145.1 (C-4a), 154.9 (C-2), 170.6 (C-6); MS, *m/e* (relative intensity) 244 (M⁺, 36), 216 (12), 162 (100), 134 (30), 94 (7), 77 (10). Anal. Calcd for $C_{15}H_{16}O_3$: C, 73.75; H, 6.60. Found: C, 73.68; H, 6.66.

4ex. White solid, mp 155−156 °C (diethyl ether); IR (KBr) *ν*: 3555 (OH), 1762 (C=O) cm⁻¹; ¹H NMR (200 MHz, CDCl₃)] δ 1.60 (s, 3H, CH_3), 1.69 (s, 3H, CH_3), 1.90−2.40 (m, 3H, H-7α, H-10α, H-10β), 2.68 (d broad, 1H, *J* = 17.6 Hz, H-7β), 3.02 (t broad, 1H, *J* = 5.5 Hz, H-6a), 3.13 (ddd, 1H, *J* = 10.9, 5.5, 5.5 Hz, H-10a), 5.90 (s broad, 1H, OH), 6.70 (dd, 1H, *J* = 7.3, 1.8 Hz, H-3), 6.88 (dd, 1H, *J* = 8.2, 1.8 Hz, H-1), 6.98 (dd, 1H, *J* = 8.2, 7.3 Hz, H-2); ¹³C NMR [50.3 MHz, CDCl₃] δ 18.7, 18.9 (8-Me, 9-Me), 30.0 (C-10), 34.6 (C-6a), 35.1 (C-7), 38.8 (C-10a), 115.0, 117.9 (C-1, C-3), 123.3, 123.5 (C-8, C-9), 124.7 (C-2), 128.9 (C-10b), 138.4 (C-4a), 143.8 (C-4), 169.5 (C-6); MS, *m/e* (relative intensity) 244 (M⁺, 46), 216 (19), 162 (100), 134 (15), 94 (10), 77 (12). Anal. Calcd for $C_{15}H_{16}O_3$: C, 73.75; H, 6.60. Found: C, 73.68; H, 6. 51.

5ex. White solid, mp 192−194 °C (CHCl₃); IR (KBr) *ν*: 3555 (OH), 1762 (C=O) cm⁻¹; ¹H NMR (200 MHz, CDCl₃)] δ 1.72 (s, 6H, 2 CH_3), 2.10−2.75 (m, 5H, H-7α, H-7β, H-6a, H-10α, H-10β), 3.01 (ddd, 1H, *J* = 11.8, 10.8, 5.5 Hz, H-10a), 5.83 (s broad, 1H, OH), 6.78 (d, 1H, *J* = 7.5 Hz, H-3), 6.91 (d, 1H, *J* = 7.7 Hz, H-1), 7.04 (t, 1H, *J* = 7.6 Hz, H-2); ¹³C NMR [50.3 MHz, CDCl₃] δ 18.7, 18.8 (8-Me, 9-Me), 32.4 (C-10), 33.4 (C-6a), 36.0 (C-7), 39.6 (C-10a), 115.0, 116.4 (C-1, C-3), 123.6, 124.4 (C-8, C-9), 124.8 (C-2), 127.2 (C-10b), 138.5 (C-4a), 143.7 (C-4), 169.6 (C-6); MS, *m/e* (relative intensity) 244 (M⁺, 46), 216 (19), 162 (100), 134 (15), 94 (10), 77 (12). Anal. Calcd for $C_{15}H_{16}O_3$: C, 73.75; H, 6.60. Found: C, 73.70; H, 6. 68.

4hy. White solid, mp 112−113 °C (lit.[6] 115−117 (n-hexane/ ethyl acetate); IR (CHCl₃) *ν*: 3270 (OH), 1754 (C=O) cm⁻¹; ¹H NMR [400 MHz, $(CD_3)_2CO$] δ 0.89 (t, 3H, *J* = 6.9 Hz, CH_3), 1.29−1.35 (m, 4H, CH_2CH_2), 1.57−1.72 (m, 3H, CH_2, H-10α), 1.63 (s, 3H, CH_3), 2.22 (dd, 1H, *J* = 5.8, 17.4, H-10β), 2.36 (d broad, 1H, H-7α), 2.51 (t broad, 2H, *J* = 7.6 HZ, ArCH_2), 2.78 (d broad, 1H, *J* = 19.8 Hz, H-7β), 3.02 (t broad, 1H, *J* = 5.8 Hz, H-6a), 3.46 (ddd, 1H, *J* = 11.5, 5.8, 5.8 Hz, H-10a), 5.41 (s broad, 1H, H-8), 6.40 (d, 1H, *J* = 2.6 Hz, H-4), 6.68 (d, 1H, *J* = 2.6 Hz, H-2), 9.07 (s broad, 1H, OH); ¹³C NMR [100.6 MHz, $(CD_3)_2CO$] δ 13.4 (C-5′), 22.2 (C-4′), 22.6 (9-Me), 24.0 (C-3′), 28.2 (C-10a), 30.7, 31.2, 32.2, 35.3 (C-1′, C-2′, C-7, C-10), 36.9 (C-6a), 107.6 (C-4), 110.8 (C-2), 113.1 (C-10b), 118.8 (C-8), 131.2 (C-9), 143.4 (C-3), 152.2 (C-4a), 153.7 (C-1), 169.6 (C-6); MS, *m/e* (relative intensity) 300 (M⁺, 29), 232 (68), 190 (18), 176 (100), 147 (7), 91 (7). Anal. Calcd for $C_{19}H_{24}O_3$: C, 75.97; H, 8.05. Found: C, 75.88; H, 8. 13.

Supporting Information Available: General experimental procedures and analytical data for all new compounds, as well as ¹H and ¹³C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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