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

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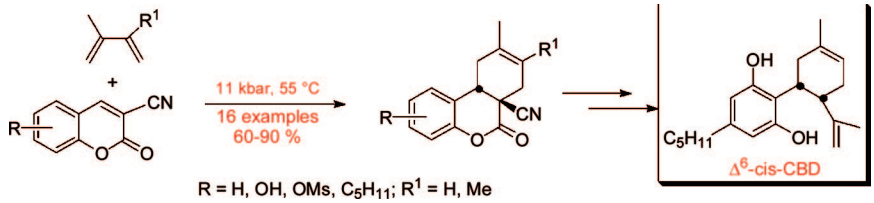

Diels−Alder cycloaddition reactions of 3-cyanocoumarin, hydroxy-substituted 3-cyanocoumarins and mesyl-substituted 3-cyano-coumarins with methyl-1,3-butadienes carried out under high pressure (11 kbar) are reported. Activation by high pressure allows these reactions to proceed satisfactorily under mild 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 Δ^6-3,4-*cis*-cannabidiol (Δ^6-*cis*-CBD) and Δ^8-*cis*-tetrahydrocannabinol (Δ^8-*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 $ZnCl_2$ as catalyst.[3] In contrast, we have shown that $HfCl_4 \cdot 2THF$ 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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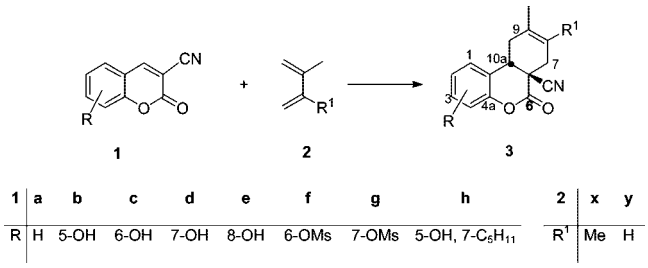
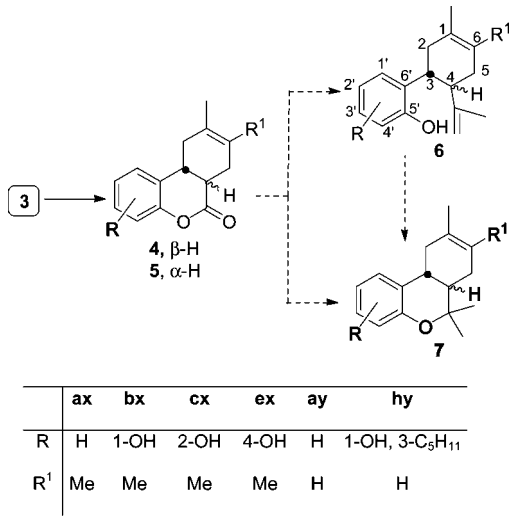
SCHEME 1. Diels-Alder Reactions between 3-Cyanocoumarins 1 and 1,3-Butadienes 2



SCHEME 2. Proposed Synthesis of Tetrahydro-6H-benzo[c]chromen-6-ones 4 and 5 and Cannabinoids 6 and 7



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 cycloaddition 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 isopropenyl-substituted tetrahydrobiaryl templates **6** and 6,6-dimethyl-tetrahydro-6H-benzo[c]chromene derivatives **7** (Scheme 2).

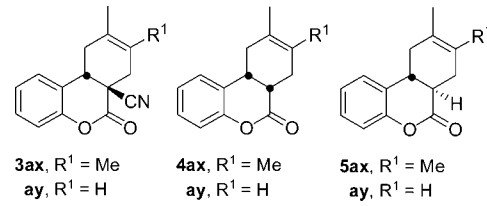
Specifically, we have apllied this approach to the synthesis of *cis*-tetrahydro-6H-benzo[c]chromen-6-one **4hy** as precursor for the synthesis of Δ^6-3,4-*cis*-cannabidiol (Δ^6-*cis*-CBD) **6hy** (R = 1′-OH, 3′-C_5H_{11}; R^1 = H), and Δ^8-*cis*-tetrahydrocannabinol (Δ^8-*cis*-THC) **7hy** (R = 1-OH, 3-C_5H_{11}; R^1 = H)[5] (Scheme 2).

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_2O	Atm	150	3	**4ax/5ax**[f,g]	65
4	**2x**	CH_2Cl_2	11	55	16	**3ax**	90
5	**2x**	MeCN	11	55	16	**3ax**	85
6	**2x**	Me_2CO	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_2O	Atm	150	3	**4ay/5ay**[f,h]	60
12	**2y**	CH_2Cl_2	11	55	16	**3ay**	85
13	**2x**	MeCN	11	55	16	**3ay**	80
14	**2y**	Me_2CO	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



Results and Discussion

Diels−Alder Reactions of 3-Cyanocoumarins 1 with 1,3-Butadienes 2. The Diels−Alder cycloadditions of 3-cyanocoumarin (**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**	CH_2Cl_2	36	**3bx**	25[d]
2	**1b**	**2x**	Me_2CO	36	**3bx**	60
3	**1b**	**2x**	MeCN	48	**3bx**	65
4	**1b**	**2y**	CH_2Cl_2	48	**3by**	30[d]
5	**1b**	**2y**	Me_2CO	36	**3by**	60
6	**1b**	**2y**	MeCN	48	**3by**	65
7	**1c**	**2x**	Me_2CO	48	**3cx**	30
8	**1c**	**2y**	Me_2CO	60	**3cy**	10[d]
9	**1d**	**2x**	MeCN	48	**3dx**	12[d]
10	**1d**	**2y**	Me_2CO	36	**3dy**	5[d]
11	**1e**	**2x**	Me_2CO	15	**3ex**	75
12	**1e**	**2y**	Me_2CO	15	**3ey**	65
13	**1f**	**2x**	MeCN	20	**3fx**	75
14	**1f**	**2y**	Me_2CO	24	**3fy**	70
15	**1g**	**2x**	MeCN	20	**3gx**	76
16	**1g**	**2y**	Me_2CO	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 ^{1}H 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.

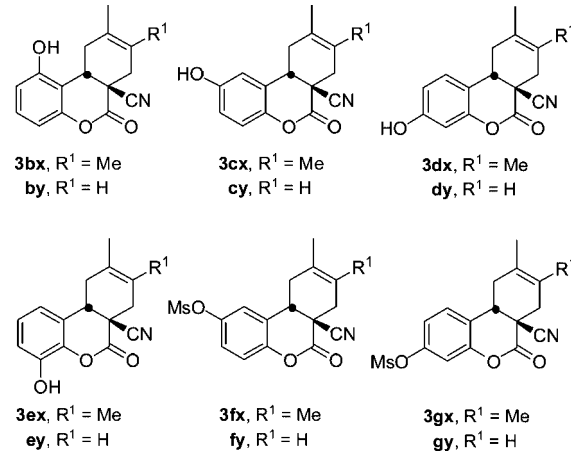
When a mixture of coumarin **1a** and 2,3-dimethyl-1,3-butadiene (**2x**) in methylene chloride was compressed to 11 kbar for 16 h at 55 °C, an isolated yield of 90% of **3ax** was obtained (Table 1, entry 4). Similarly, isoprene (**2y**) under identical conditions gave **3ay** in high yield (85%) (Table 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 these substrates by the hydroxy group in the 6- and 7-positions, respectively.

SCHEME 4



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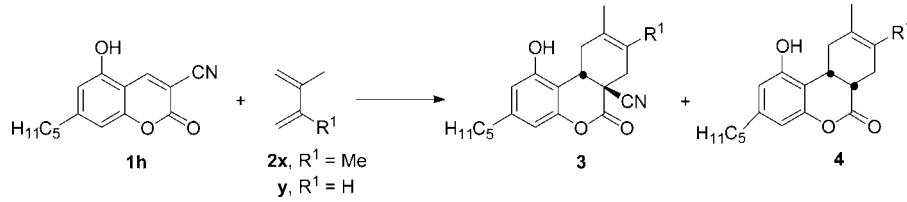
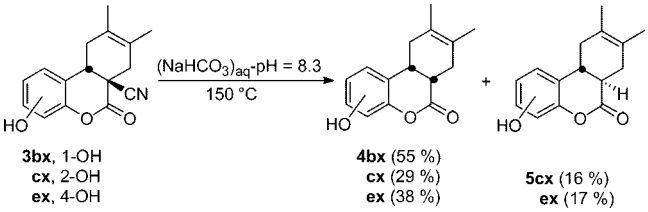
TABLE 3. Diels−Alder Reactions of Coumarin (1h) with 2,3-Dimethyl-1,3-butadiene (2x) and Isoprene (2y) under Atmospheric and 11 kbar Pressure Conditions



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_2Cl_2	11	55	16	**3hx**	68
3	**2y** (3)	H_2O	Atm.	150	2	**3hy**	30
4	**2y** (3)	H_2O	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_2Cl_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 ^1H NMR characterization has been reported. The structure and stereochemistry of the products were assigned by analyzing the ^1H 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

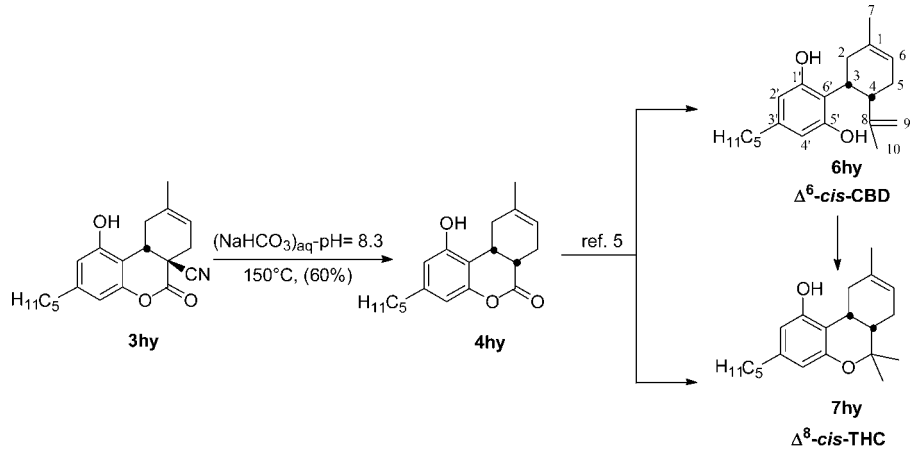


TABLE 4. $^3J_{H,H}$ Coupling Constant Values (Hz) of H(10a) of Compounds 4 and 5

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, $CDCl_3$) *δ* 1.65 (s, 6H, 2 CH_3), 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-10*β*), 2.55 (d broad, 1H, *J* = 17.3 Hz, H-7α), 2.85 (d broad, 1H, *J* = 17.3 Hz, H-7*β*), 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); ^{13}C NMR (50.3 MHz, $CDCl_3$) *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 $C_{16}H_{15}NO_2$: 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, $CDCl_3$) *δ* 1.66 (s, 3H, CH_3), 2.17 (dd broad, 1H, *J* = 18.3, 8.0 Hz, H-10α), 2.36−2.64 (m, 2H, H-7α, H-10*β*), 2.85 (dddd, 1H, *J* = 17.6, 7.6, 3.7, 1.9 Hz, H-7*β*), 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); ^{13}C NMR (50.3 MHz, $CDCl_3$) *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 $C_{15}H_{13}NO_2$: 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 ($CHCl_3$) *ν*: 2242 (CN), 1780 (C═O) cm^{-1}; ^1H NMR [400 MHz, $(CD_3)_2CO$] *δ* 1.62 (s, 3H, CH_3), 1.72 (s, 3H, CH_3), 1.84 (m broad, 1H, H-10α), 2.41 (dd, 1H, *J* = 18.2, 6.2 Hz, H-10*β*), 2.80 (d broad, 1H, *J* = 17.6 Hz, H-7α), 3.05 (d broad, 1H, *J* = 17.6 Hz, H-7*β*), 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); ^{13}C NMR [100.6 MHz, $(CD_3)_2CO$] *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 $C_{16}H_{15}NO_3$: 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, $(CD_3)_2CO$] *δ* 1.67 (s, 3H, CH_3), 1.83 (m broad, 1H, H-10α), 2.45 (dd, 1H, *J* = 17.8, 5.8 Hz, H-10*β*), 2.80 (d broad, 1H, *J* = 18.4 Hz, H-7*β*), 3.19 (d broad, 1H, *J* = 18.4 Hz, H-7*β*), 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); ^{13}C NMR [100.6 MHz,

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

$(CD_3)_2CO$] 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}; ^1H NMR [400 MHz, $(CD_3)_2CO$] 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, $(CD_3)_2CO$] 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}; ^1H NMR [400 MHz, $(CD_3)_2CO$] 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, $(CD_3)_2CO$] 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}; ^1H NMR [400 MHz, $(CD_3)_2CO$] 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, $(CD_3)_2CO$] 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}; ^1H NMR [400 MHz, $(CD_3)_2CO$] 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, $(CD_3)_2CO$] δ 18.3, 18.7 (8-Me, 9-Me), 32.6, 34.9 (C-7, C-10), 37.5 (OSO_2CH_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 $C_{17}H_{17}NO_5S$: 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}; ^1H NMR [400 MHz, $(CD_3)_2CO$] 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, $(CD_3)_2CO$] δ 23.2 (9-Me), 29.6, 30.7 (C-7, C-10), 37.3 (OSO_2CH_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 $C_{16}H_{15}NO_5S$: 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}; ^1H NMR [400 MHz, $(CD_3)_2CO$] 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_2CH_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, $(CD_3)_2CO$] δ 17.4, 17.8 (8-Me, 9-Me), 31.8, 33.9 (C-7, C-10), 36.4 (C-10a), 36.9 (OSO_2CH_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 $C_{17}H_{17}NO_5S$: 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}; ^1H NMR [400 MHz, $(CD_3)_2CO$] 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_2CH_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, $(CD_3)_2CO$] δ 22.4 (9-Me), 28.8, 29.9 (C-7, C-10), 36.2 (C-10a), 37.0 (OSO_2CH_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 $C_{16}H_{15}NO_5S$: 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}; ^1H NMR [200 MHz, ($CDCl_3$] δ 0.89 (s, 3H, CH_3), 1.10−1.45 (m, 4H, CH_2CH_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}; ^1H NMR [200 MHz, ($CDCl_3$] δ 0.94 (s, 3H, CH_3), 1.10−1.50 (m, 4H, CH_2CH_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-10*β*), 2.66 (d broad, 1H, *J* = 17.8 Hz, H-7*β*), 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); ^{13}C 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, $CDCl_3$)] *δ* 1.58 (s, 3H, CH_3), 1.66 (s, 3H, CH_3), 1.87−2.37 (m, 3H, H-7α, H-10α, H-10*β*), 2.65 (d broad, 1H, *J* = 17.7 Hz, H-7*β*), 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); ^{13}C NMR [50.3 MHz, $CDCl_3$] *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-7*β*, H-6a, H-10α, H-10*β*), 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); ^{13}C 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, $CDCl_3$)] *δ* 1.60 (s, 3H, CH_3), 1.69 (s, 3H, CH_3), 1.90−2.40 (m, 3H, H-7α, H-10α, H-10*β*), 2.68 (d broad, 1H, *J* = 17.6 Hz, H-7*β*), 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); ^{13}C NMR [50.3 MHz, $CDCl_3$] *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 ($CHCl_3$); IR (KBr) *ν*: 3555 (OH), 1762 (C═O) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$)] *δ* 1.72 (s, 6H, 2 CH_3), 2.10−2.75 (m, 5H, H-7α, H-7*β*, H-6a, H-10α, H-10*β*), 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); ^{13}C NMR [50.3 MHz, $CDCl_3$] *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 ($CHCl_3$) *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-10*β*), 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-7*β*), 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); ^{13}C 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.

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Supporting Information Available: General experimental procedures and analytical data for all new compounds, as well as ^1H and ^{13}C 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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