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High-Pressure Diels−Alder Cycloadditions between Benzylideneacetones and 1,3-Butadienes: Application to the Synthesis of (*R*,*R*)-(−)- and (*S*,*S*)-(+)-Δ^8-Tetrahydrocannabinol

Eleonora Ballerini, Lucio Minuti,* and Oriana Piermatti

Dipartimento di Chimica, Università degli Studi di Perugia, via Elce di Sotto 8, 06123 Perugia, Italy

lucio@unipg.it

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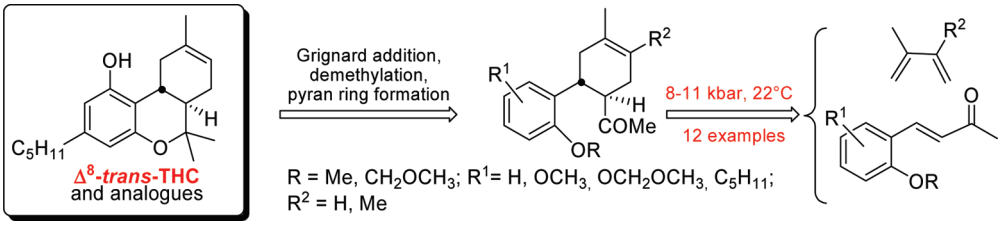

High-pressure Diels−Alder reactions of various alkoxy/alkyl-substituted benzylideneacetones with methyl-1,3-butadienes are reported. Activation by high pressure (8−11 kbar) in combination with the mild Lewis acid $HfCl_4 \cdot 2THF$ allows these reactions to efficiently and regioselectively produce a series of ortho-substituted cyclohexenyl-benzene cycloadducts, that are useful precursors for the expeditious construction of the *privileged* 6,6-dimethyltetrahydro-6*H*-benzo[*c*]chromene skeleton. Application to the synthesis of Δ^8-*trans*-THC in both enantiomeric pure forms is based on the successful resolution of selected cycloadduct by the SAMP−hydrazone method.

Introduction

The 6,6-dimethyltetrahydro-6*H*-benzo[*c*]chromene system occurs in a wide variety of natural products with diverse biological activities; it has been selected as a *privileged structure* due to its capacity to interact with a variety of cellular targets.[1] Representative examples of natural products possessing this *privileged* structural motif include the Cannabinoids (i.e., Δ^9-THC **1** and Δ^8-THC **2**) (Figure 1), a well-known group of structurally related natural products, that have been isolated from *Cannabis sativa var. indica*.[2] Their

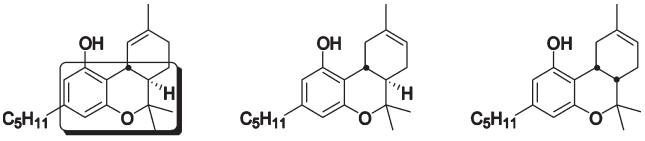

FIGURE 1. Tetrahydrocannabinol (THC) family.

potent bioactivities have stimulated the development of many synthesis and pharmacological investigations.[3] Extensive Structure Activity Relationship (SAR) studies have highlighted the need to develop a flexible synthetic route that will allow target compounds to be produced easily, in high yields, and in stereochemically pure form.

*To whom correspondence should be addressed. Phone: +39.075.5855545. Fax: +39.075.5855560.

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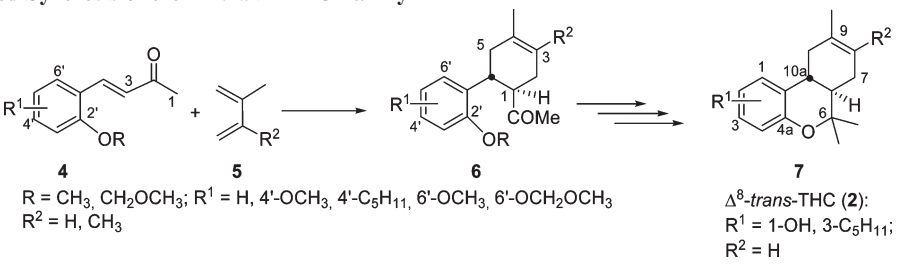
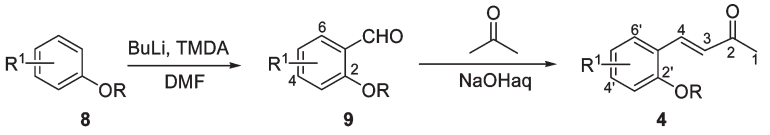
SCHEME 1. Proposed Synthesis of the Δ^8-*trans*-THC Family



SCHEME 2. Synthesis of Benzylideneacetones



	a	b	c	d	e	f
R	CH_3	CH_3	CH_3	CH_2OCH_3	CH_3	CH_2OCH_3
R^1	H	4'-OCH_3	6'-OCH_3	6'-OCH_2OCH_3	4'-C_5H_{11}, 6'-OCH_3	4'-C_5H_{11}, 6'-OCH_2OCH_3

Previous reports from this laboratory described a new and environmentally safe method for building the tetrahydro-6*H*-benzo[*c*]chromene structural unit by Diels−Alder reactions of low reactive 3-substituted coumarins with methyl-1,3-butadienes.[4] These studies have demonstrated the benefits of using high pressure as the activating method in the Diels−Alder strategy to obtain polysubstituted benzo[*c*]-chromene templates, under milder conditions without the use of a metallic catalyst, thus highlighting the high-pressure technology as a valuable tool in eco-friendly processes.[5] Using hydroxy-substituted 3-cyanocoumarins as dienophiles, we have developed a Diels−Alder strategy for synthesizing a range of hydroxy-substituted *cis*-6a-cyanobenzo[*c*]chromenones and have applied it to the synthesis of Δ^6-3,4-*cis*-cannabidiol and Δ^8-*cis*-tetrahydrocannabinol (**3**), in order to open a route to the non-natural Δ^8-*cis*-tetrahydrocannabinol family.[4b]

Most natural tetrahydrocannabinol products, such as (−)-Δ^9-THC (**1**) and (−)-Δ^8-THC (**2**), have a trans stereochemistry at the cyclohexene ring, instead of the *cis*-fused ring system that was obtained with our reported strategy.

Various syntheses of compounds belonging to the natural *trans*-THC family have been reported, but almost all of the strategies are based on the condensation of a proper aromatic ring system, with chiral building blocks available from chiral pool-based monoterpenes. Most strategies suffer from serious drawbacks such as harsh reaction conditions, low yields, and little flexibility and therefore great difficulty in constructing libraries of cannabinoid analogues and other new natural product-like compounds.[3,6] We envisioned a new eco-friendly method for constructing the 6,6-dimethyl-tetrahydro-6*H*-benzo[*c*]chromene skeleton, including the Δ^8-*trans*-THC (**2**). The strategy is based on a Diels−Alder reaction of alkoxy/alkyl-substituted benzylideneacetones **4** with 1,3-butadienes (**5**) followed by Grignard addition, demethylation, and cyclization (Scheme 1).

It was obvious that the success of the plan would primarily hinge on whether the deactivated di- and trisubstituted (R = CH_2OCH_3, CH_3; R^1 = H, OCH_2OCH_3, OCH_3, C_5H_{11}) benzylideneacetones **4** could be made to react with methyl-1,3-butadienes (**5**).

Thus, in continuation to our research directed toward the synthesis of compounds that incorporate the benzo[*c*]-chromene subunit, we here report (i) the study of the Diels−Alder reaction of benzylideneacetones **4** with 1,3-butadienes **5** (Scheme 1) and (ii) the conversion of selected cycloadducts **6** into their corresponding racemic Δ^8-*trans*-THC (**2**) along with their non-natural analogues **7**. We also report an efficient protocol for obtaining Δ^8-*trans*-THC **2** in both enantiomeric pure forms (Scheme 1).

Results and Discussion

Benzylideneacetone Synthesis. The necessary benzylideneacetones **4** can be readily synthesized in high yields

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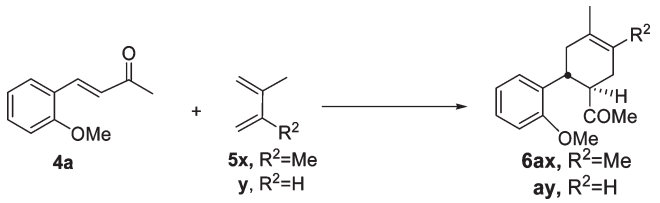
TABLE 1. Diels–Alder Reactions of 2′-Methoxybenzylideneacetone (4a) with 2,3-Dimethyl-1,3-butadiene (5x) and Isoprene (5y) under Atmospheric and High-Pressure Conditions



entry	diene[a]	medium[b]	time (h)	pressure (kbar)	temp (°C)	catalyst[c]	product	yield[d] (%)
1	**5x**	CH_2Cl_2	115	atm	50		**6ax**	
2	**5x**	PhMe	115	atm	110		**6ax**	
3	**5x**	H_2O	52	atm	150		**6ax**	43[e]
4	**5x**[f]	SolFC	48	atm	110		**6ax**	45[e]
5	**5x**	CH_2Cl_2	48	atm	50	$HfCl_4 \cdot 2THF$	**6ax**	49
6	**5x**	CH_2Cl_2	70	10	50		**6ax**	41
7	**5x**	CH_2Cl_2	16	8	22	$HfCl_4 \cdot 2THF$	**6ax**	92
8	**5x**	CH_2Cl_2	16	8	22	$HfCl_4 \cdot 2THF$[g]	**6ax**	80
9	**5x**	CH_2Cl_2	16	8	22	$AlCl_3 \cdot 2THF$	**6ax**	85
10	**5x**	CH_2Cl_2	16	8	22	$Sc(OTf)_3$	**6ax**	55
11	**5x**	CH_2Cl_2	16	8	22	$EtAlCl_2$		
12	**5x**	CH_2Cl_2	16	8	22	$AlCl_3$		
13	**5y**	PhMe	115	atm	110			
14	**5y**	H_2O	72	atm	150		**6ay**	32[e]
15	**5y**[f]	SolFC	52	atm	110		**6ay**	35[e]
16	**5y**	CH_2Cl_2	55	atm	50	$HfCl_4 \cdot 2THF$	**6ay**	45
17	**5y**	CH_2Cl_2	70	10	50		**6ay**	28[e]
18	**5y**	CH_2Cl_2	16	8	22	$HfCl_4 \cdot 2THF$	**6ay**	85
19	**5y**	CH_2Cl_2	16	8	22	$HfCl_4 \cdot 2THF$[g]	**6ay**	74

[a]3 equiv of 1,3-diene was used. [b]Concentration of **1a** = 0.1 M. [c]10 mol % of catalyst was used. [d]Yields of isolated cycloadducts. [e]Conversion determined by ^1H NMR of crude reaction mixture. [f]10 equiv of 1,3-diene was used. [g]25 mol % of catalyst was used.

(80–93%) and with total selectivity by aldol condensation of benzaldehydes **9** and acetone[7] (Scheme 2). While **9a–c** are commercially available aldehydes, the others were prepared by formylation reaction of the corresponding benzene derivatives **8d–f**.[3h,4b] The (*E*)-configuration of the carbon–carbon double bond for all benzylideneacetones **4** was confirmed from the 16.4–16.6 Hz coupling constant values measured for $^3J_{3,4}$.

Diels–Alder Reaction of Benzylideneacetones 4 with 1,3-Butadienes 5. The Diels–Alder cycloadditions of benzylideneacetones are still scarcely explored, owing to the low reactivity of the benzylideneacetone double bond. For example, thermal reaction of unsubstituted benzylideneacetone with cyclopentadiene or 2-(diphenylphosphinyl)-1,3-butadiene under atmospheric pressure gives only low to moderate yields of mixtures of the corresponding adducts (35–64% and 30–38%, respectively),[8] while with cyclohexadiene a satisfactory yield was obtained when the reaction was performed under 13 kbar of pressure and in the presence of $Yb(OTf)_3$ catalyst.[9] Our synthetic plan requires the use of alkoxy/alkyl-substituted benzylideneacetones which are deactivated as dienophiles in the Diels–Alder reaction by the electron-donating alkoxy/alkyl groups in the 2′-, 4′-, and 6′-positions. However, to the best of our knowledge, no examples of Diels–Alder reaction between 1,3-butadienes and alkoxy/alkyl-substituted benzylideneacetones have been reported except the cycloaddition reaction between benzylideneacetone **4e** and isoprene **5y** that reportedly occurs in the autoclave at high temperature (185 °C) to give an unspecified mixture of two compounds.[10]

Thus, the reactions of 2′-methoxybenzylideneacetone **4a** with dienes **5x,y** were chosen as the initial model for our system and investigated under atmospheric and high-pressure conditions. The results of the optimization study are summarized in Table 1.

Under atmospheric pressure, the reaction of 2′-methoxybenzylideneacetone (**4a**) with both dienes **5** did not occur when performed for a long time (115 h) at 50 °C in methylene chloride or at 110 °C in toluene (Table 1, entries 1, 2, and 13). A low conversion of **4a** to **6ax** or **6ay** (32–49%) was obtained under aqueous or solvent-free conditions at 150 and 110 °C, respectively (Table 1, entries 3, 4, 14, and 15), or by heating **4a** and dienes **5** in methylene chloride at 50 °C in the presence of $HfCl_4 \cdot 2THF$ (Table 1, entries 5 and 16).

The unsatisfactory results (low conversions and/or high temperature and long reaction time) obtained under normal pressure conditions make the procedure unsuitable on sensitive substrates and in the total synthesis of natural and non-natural products. Considering the powerful pressure-induced acceleration of the Diels–Alder reactions,[4,5] we studied the cycloadditions of 2′-methoxybenzylideneacetone (**4a**) with dienes **5** under high pressure in an effort to find more efficient and eco-friendly conditions for these transformations.

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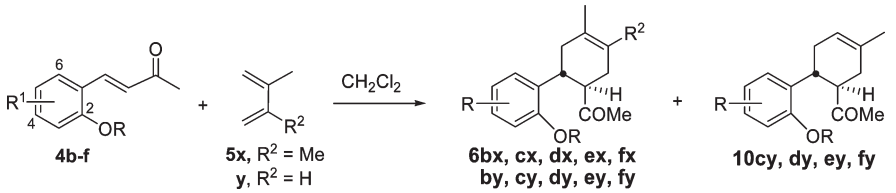
(10) Korte, F.; Dlugosch, E.; Claussen, U. *Liebigs Ann. Chem.* **1965**, *685*, 2210–2214. When we repeated the reaction between **4e** and **5y** under the reaction conditions described in this paper a 1.5:1 mixture of the regioisomers **6ey**/**10ey** was obtained with a 36% yield, lower than that reported by the authors (72%).

TABLE 2. Diels−Alder Reactions of Benzylideneacetones 4b−f with 2,3-Dimethyl-1,3-butadiene (5x) and Isoprene (5y)



entry	dienophile[a]	diene[b]	*t* (h)	*P* (kbar)	*T* (°C)	catalyst[c]	products	yield[d] (%)
1	**4b**	**5x**	130	atm	50	$HfCl_4 \cdot 2THF$	**6bx**	<5[e]
2	**4b**	**5x**	16	11	22	$HfCl_4 \cdot 2THF$	**6bx**	81
3	**4b**	**5x**	16	11	22	$AlCl_3 \cdot 2THF$	**6bx**	75
4	**4b**	**5x**	24	11	22	$Sc(OTf)_3$[f]	**6bx**	55[e]
5	**4b**	**5y**	130	atm	50	$HfCl_4 \cdot 2THF$	**6by**	<5[e]
6	**4b**	**5y**	20	11	22	$HfCl_4 \cdot 2THF$	**6by**	81
7	**4b**	**5y**	20	10	22	$AlCl_3 \cdot 2THF$	**6by**	68
8	**4c**	**5x**	22	11	22	$HfCl_4 \cdot 2THF$	**6cx**	70
9	**4c**	**5y**	72	11	50		**6cy/10cy** (1.5:1)[g]	28
10	**4c**	**5y**	22	11	22	$HfCl_4 \cdot 2THF$	**6cy/10cy** (16:1)[g]	80
11	**4c**	**5y**	24	11	22	$AlCl_3 \cdot 2THF$	**6cy/10cy** (22/1)[g]	70
12	**4d**	**5x**	130	atm	50	$HfCl_4 \cdot 2THF$	**6dx**	<5[e]
13	**4d**	**5x**	24	11	22	$HfCl_4 \cdot 2THF$	**6dx**	71
14	**4d**	**5y**	130	atm	50	$HfCl_4 \cdot 2THF$	**6dy**	<5[e]
15	**4d**	**5y**	72	11	50		**6dy/10dy** (1:1)[g]	25
16	**4d**	**5y**	16	11	22	$HfCl_4 \cdot 2THF$	**6dy/10dy** (7:1)[g]	84
17	**4d**	**5y**	22	11	22	$AlCl_3 \cdot 2THF$	**6dy/10dy** (24/1)[g]	75
18	**4d**	**5y**	16	11	22	$Yb(OTf)_3$	**6dy/10dy** (9:1)[g]	60
19	**4e**	**5x**	20	11	22	$HfCl_4 \cdot 2THF$	**6ex**	75
20	**4e**	**5y**	24	11	22	$HfCl_4 \cdot 2THF$	**6ey/10ey** (12:1)[g]	80[10]
21	**4e**	**5y**	24	11	22	$AlCl_3 \cdot 2THF$	**6ey/10ey** (24/1)[g]	72
22	**4e**	**5y**	24	11	22	$Yb(OTf)_3$	**6ey/10ey** (15/1)[g]	60
23	**4f**	**5x**	18	11	22	$HfCl_4 \cdot 2THF$	**6fx**	72
24	**4f**	**5y**	24	11	22	$HfCl_4 \cdot 2THF$	**6fy/10fy** (11:1)[g]	73
25	**4f**	**5y**	20	11	22	$AlCl_3 \cdot 2THF$	**6fy/10fy** (18/1)[g]	62

[a]Concentration of dienophile = 0.1 M. [b]3 equiv of 1,3-diene was used. [c]10 mol % of catalyst was used. [d]Yields of isolated cycloadducts. [e]Conversion determined by ^1H NMR of crude reaction mixture. [f]25 mol % of catalyst was used. [g]Regioisomeric ratio was determined by GC and ^1H NMR analyses.

When a mixture of **4a** and 2,3-dimethyl-1,3-butadiene (**5x**) in methylene chloride was compressed to 10 kbar for 70 h at 50 °C, a 41% isolated yield of **6ax** was obtained (Table 1, entry 6). Similarly, under identical conditions isoprene (**5y**) gave **6ay** in low yield (28%) (Table 1, entry 17). Activation by high pressure in combination with Lewis acid catalysis allowed the same reactions to proceed satisfactorily under much milder conditions. Indeed, using hyperbaric conditions (8 kbar) and the mild Lewis acid $HfCl_4 \cdot 2THF$ (10 mol %) the cycloadditions of **4a** with **5x** at room temperature (22 °C) occurred in a shorter reaction time (16 h) with good yields (92%) (Table 1, entry 7). Under identical conditions, isoprene (**5y**) gave **6ay** regioselectively and in high yield (85%) (Table 1, entry 18). In the case of the 8 kbar pressure cycloaddition of **4a** with **5x**, the use of $AlCl_3 \cdot 2THF$ gave a slightly reduced yield (85%) (Table 1, entry 9), whereas $Sc(OTf)_3$ gave a low yield (55%) (Table 1, entry 10). The use of conventional Lewis acids, such as $EtAlCl_2$ and $AlCl_3$, resulted in an extensive polymerization (Table 1, entries 11 and 12). Thus, it was found that the hafnium(IV) or aluminum catalyst, when used as THF-complex salts, is essential for the current reactions at high pressure. To the best of our knowledge the catalytic efficiency of $HfCl_4 \cdot 2THF$ and $AlCl_3 \cdot 2THF$ in high-pressure Diels−Alder reactions has never been reported[5] and may be ascribed to their great ability to coordinate the carbonyl oxygen of **4a** together with the air-stability and ease-of-use of these THF-complex salts, which limit the polymerization of diene.

In view of these results, the study was extended to the Diels−Alder reactions of dialkoxy-substituted benzylideneacetones **4b−f** to determine the scope of the reaction (Table 2 and Figure 2). The alkoxy group in the 2′-position of benzylideneacetones is essential for the pyran ring formation of the THC family (see Scheme 1), whereas those in 4′- or 6′-positions are useful to have access to desoxy-cannabinoids and to the characteristic 1-hydroxy group of cannabinoids, respectively (Figure 1).

Under atmospheric conditions, the $HfCl_4 \cdot THF$-catalyzed cycloadditions of **4b** or **4d** with both dienes **5** at 50 °C for a long time (130 h) gave a negligible (<5%) conversion (Table 2, entries 1, 5, 12, and 14). This was the result of the deactivation of the dienophilic components **4b** and **4d** with respect to **4a** by the two alkoxy groups and illustrates the need for the hyperbaric conditions. Thus, when the $HfCl_4 \cdot THF$-catalyzed cycloadditions of **4b−f** with **5x** were compressed to 11 kbar for 16−24 h at 22 °C, the corresponding cycloadducts were given in satisfactory yields (70−81%) (Table 2, entries 2, 8, 13, 19, and 23). With isoprene (**5y**), the cycloaddition of **4b** regioselectively produced the adduct **6by** in 81% yield (Table 2, entry 6), whereas the cycloadditions of **4c−f** gave good yields (73−84%), but were less regioselective producing mixtures of para/meta adducts **6cy**/**10cy**, **6dy**/**10dy**, **6ey**/**10ey**, and **6fy**/**10fy** (Figure 2) in ratios 16/1, 7/1, 12/1, and 11/1, respectively (Table 2, entries 10, 16, 20, and 24). To obtain more information about the parameters that control the regioselectivity, the cycloaddition

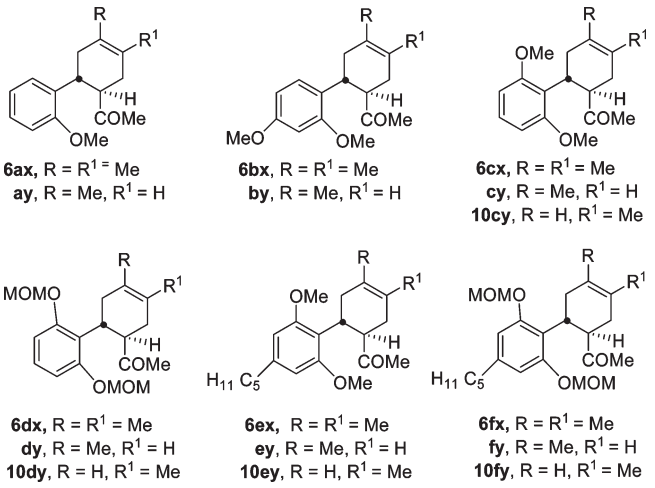


FIGURE 2. Diels−Alder cycloadducts.

reactions with isoprene (**5y**) were also investigated by using high-pressure activation alone or high pressure in combination with the mild Lewis acids $AlCl_3 \cdot 2THF$ or $Yb(OTf)_3$. At 50 °C, the uncatalyzed 11 kbar pressure reactions of **5y** with **4c** and **4d** both gave poor yields (< 30%) and poor regioselectivities (Table 2, entries 9 and 15). However, compared to the $HfCl_4 \cdot THF$-catalyzed reactions, the use of $AlCl_3 \cdot 2THF$ in the 11 kbar pressure cycloadditions of isoprene (**5y**) with **4c**−**f** led to a significant increase in regioselectivity, but slightly lower yields of the corresponding cycloadducts **6** and **10** (Table 2, entries 11, 17, 21, and 25). Under 11 kbar of pressure, the use of $Yb(OTf)_3$ in the reactions of **5y** with **4d** and **4e** led to lower yields and less regioselectivity compared to $AlCl_3 \cdot 2THF$ (Table 2, entries 18 and 22).

Application to the Synthesis of the Δ^8-THC Family. With the alkoxy-substituted cyclohexenylbenzenes **6** in hand, we then turned our attention to the synthesis of Δ^8-THC (**2**) and its anologues **7**. The next step toward the synthesis of the Δ^8-THC family was the Grignard addition to the carbonyl carbon of cycloadducts **6**, followed by the removal of the protective groups on the aromatic ring and subsequent construction of the pyran ring (see abstract). Among the cycloadducts **6**, compounds **6dy** and **6fy** with the MOM protection on the aromatic part were initially chosen because

TABLE 3. Attempted Deprotection/Cyclization on 11 and 12

entry	reagent	conditions	result
1	**11a**	THF, 2-Propanol, HCl_{conc}, rt, 24 h	mixture
2	**11a**	MeOH, *p*-TsOH, 30 °C, 21 h	mixture
3	**11a**	NaSEt, DMF, 140 °C, 7 h	NR[a]
4	**11b**	$NaHSO_4 \cdot SiO_2$, CH_2Cl_2, rt, 2 h	mixture
5	**11b**	$BF_3 \cdot Et_2O$, CH_2Cl_2, rt, 5 h	mixture
6	**11b**	MeOH, *p*-TsOH, 30 °C, 3 h	NR[a]
7	**11b**	catecholborane, CH_2Cl_2, 0 °C, 1 h	mixture
8	**12**	THF, 2-propanol, HCl_{conc}, rt, 10 h	mixture
9	**12**	$NaHSO_4 \cdot SiO_2$, CH_2Cl_2, rt, 5 h	mixture
10	**12**	$BF_3 \cdot Et_2O$, CH_2Cl_2, rt, 5 h	mixture

[a]NR: no reaction.

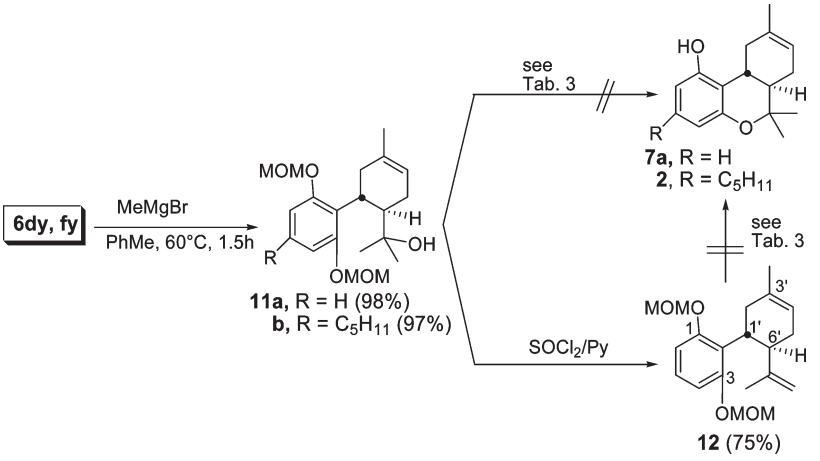
it was expected that under the acidic reaction conditions, the tertiary alcohols **11a**,**b**, obtained by methylation of adducts **6dy** and **6fy**, would undergo deprotection of both MOM groups and simultaneous cyclization to give the pyran ring in one step (Scheme 3). Thus, the addition of MeMgBr to the cycloadducts **6dy** and **6fy** at 60 °C resulted in the formation of the corresponding tertiary alcohols **11a** and **11b** in good yields (98% and 97%, respectively) (Scheme 3).

However, every attempt to achieve a one-step deprotection of both protecting groups or deprotection/cyclization on **11a**,**b** was unsuccessful. Alcohols **11a**,**b** were treated with various acidic reagents (Table 3, entries 1−7), and **11a** was converted to the cannabidiene **12** and then treated with acidic reagents (Table 3, entries 8−10), but no reagents provided the desidered products **2** and **7a**,.

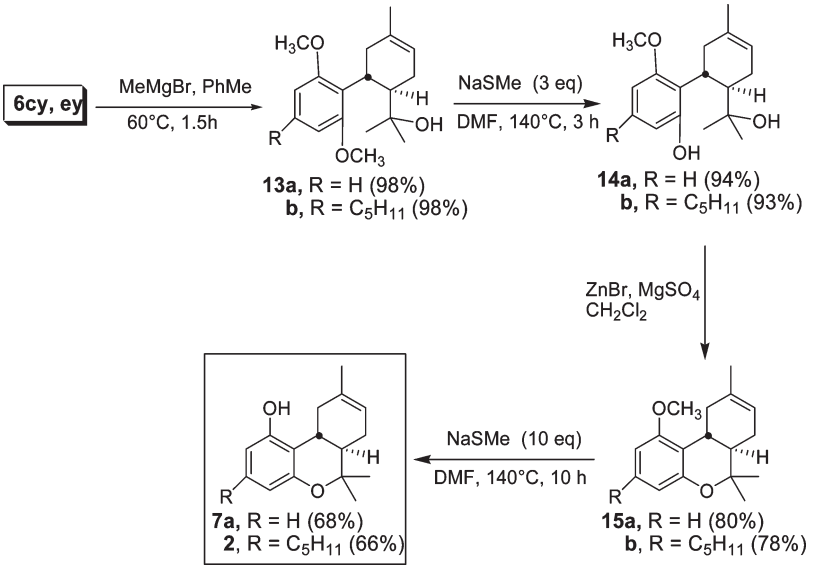
We then decided to carry out the deprotection/cyclization on tertiary alcohols **13a**,**b**, obtained by adding MeMgBr to the O-methylated cycloadducts **6cy** and **6ey** (Scheme 4).

When the dimethylethers **13a**,**b** were treated with NaSMe in DMF according to Feutrill,[11] monodemethylation occurred to furnish the corresponding diols **14a**,**b**[12] (Scheme 4). The formation of cyclized ethers **15a**,**b** was then achieved in high yields (80% and 78%, respectively) by treating **14a**,**b** with $ZnBr_2$ in the presence of $MgSO_4$ according to the literature data.[6g,3e,h] The remaining methoxy group on **15a**,**b** was then removed with NaSMe (10 equiv) in DMF at 140 °C to afford the desidered Δ^8-*trans*-THC (**2**) and the 6a,7,10,10a-tetrahydro-6,6,9-trimethyl-6*H*-benzo[*c*]chromen-1-ol (**7a**) in 66% and 68% yields, respectively. The Δ^8-THC (**2**) synthesized in our laboratory was characterized by ^1H and ^{13}C NMR, IR, and MS spectra. The ^1H NMR (400 MHz)

SCHEME 3. Attempts to Synthesize Δ^8-THCs 2 and 7a



SCHEME 4. Racemic Synthesis of Δ^8-THCs 2 and 7a



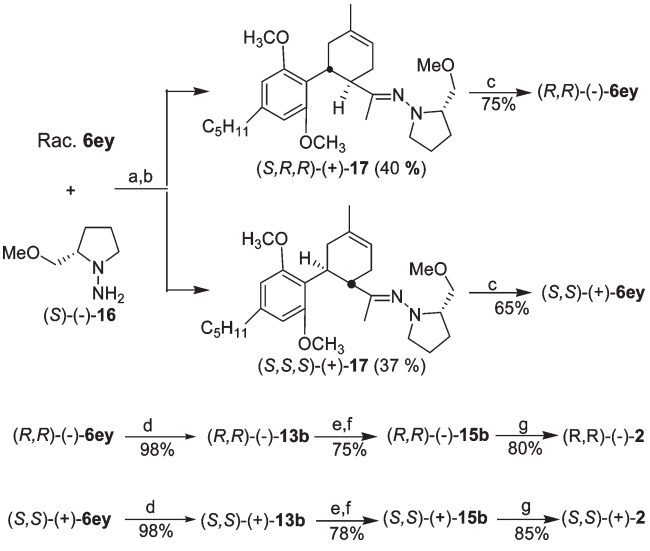
spectrum was identical with that (60 MHz) previously reported for the natural Δ^8-THC (**2**).[6a−d]

Synthesis of (*R*,*R*)-(−)- and (*S*,*S*)-(+)-Δ^8-THCs (2). Having synthesized racemic Δ^8-THC (**2**), we then developed an efficient protocol to obtain enantiomerically enriched Δ^8-THCs. The procedure is based on the resolution of the cycloadduct **6ey** by applying the SAMP-hydrazone method.[13] The acetyl derivative **6ey** was treated with commercially available (*S*)-(−)-1-amino-2-(methoxymethyl)pyrrolidine (SAMP) (**16**) to obtain a mixture of the two diastereoisomeric SAMP-hydrazones **17**. The mixture was chromatographed over silica gel, eluting with 9:1 petroleum ether/Et_2O to give diastereomerically pure (*S*,*R*,*R*)-(+)-**17** ($[\alpha]_D$ +73 (*c* 1.99, $CHCl_3$)) and (*S*,*S*,*S*)-(+)-**17** ($[\alpha]_D$ +115 (*c* 1.28, $CHCl_3$)) in 40% and 37% yield, respectively. Enantiomerically pure (*R*,*R*)-(−)-**6ey** ($[\alpha]_D$ −23 (*c* 1.34, $CHCl_3$)) and (*S*,*S*)-(+)-**6ey** ($[\alpha]_D$ +22 (*c* 0.6, $CHCl_3$)) were obtained in 75% and 65% yield, respectively, upon hydrolysis of the corresponding SAMP-hydrazones **17** with oxalic acid. It should be noted that the SAMP (**16**) was recovered in 70% yield. Confirmation that no racemization had occurred under the reaction conditions was achieved by reamination of (*R*,*R*)-(−)-**6ey** with (*S*)-(−)-SAMP **16** to provide (*S*,*R*,*R*)-(+)-**17** as a single diastereomer (85%).

With the same sequence established for the synthesis of racemic Δ^8-THC **2**, the (*R*,*R*)-(−)-Δ^8-THC **2** ($[\alpha]_D$ −245 (*c* 0.78, $CHCl_3$)) and (*S*,*S*)-(+)-Δ^8-THC **2** ($[\alpha]_D$ +240 (*c* 0.94, $CHCl_3$)) were prepared from (*R*,*R*)-(−)-**6ey** and (*S*,*S*)-(+)-**6ey**, respectively, through the key intermediates (*R*,*R*)-(−)-**13b** ($[\alpha]_D$ −13 (*c* 1.28, $CHCl_3$)) and (*S*,*S*)-(+)-**13b** ($[\alpha]_D$ +15 (*c* 0.78, $CHCl_3$)), and (*R*,*R*)-(−)-**15b** ($[\alpha]_D$ −178 (*c* 0.65, $CHCl_3$)) and (*S*,*S*)-(+)-**15b** ($[\alpha]_D$ +178 (*c* 0.545, $CHCl_3$)) (Scheme 5).

Structural Analysis. All compounds were purified by column chromatography or by recrystallization with the exception of **10cy**−**fy**. All attempts to isolate these compounds in pure form were unsuccessful; their structures were assigned by using enriched mixtures. The complete ^1H NMR assignments, as well as the *trans*-stereochemical assignment, were based on the relevant ^1H NMR coupling constant value and on 2D-COSY, NOESY, HMQC, and HMBC[14] experiments. The (*E*)-configuration of all benzylideneacetones **4** was confirmed from 16.4 to 16.6 Hz coupling constant values

SCHEME 5. Resolution of Racemic 6ey via SAMP Derivatization and Synthesis of (*R*,*R*)-(−)- and (*S*,*S*)-(+)-Δ^8-THCs 2[a]



[a]Reagents and conditions: (a) *p*-TsOH, heptane, 100°C, 47 h; (b) column chromatography; (c) Et_2O, aqueous oxalic acid, rt, 4 d; (d) MeMgBr, toluene, 60°C, 1,5 h; (e) 3 equiv of NaSMe, DMF, 140°C, 3 h; (f) $ZnBr_2$, $MgSO_4$, CH_2Cl_2, rt, 15 h; (g) 10 equiv of NaSMe, DMF, 140°C, 10 h.

(11) Feutrill, G. I.; Mirrington, R. N. *Tetrahedron Lett*. **1970**, 1327–1328.
(12) Compounds **14a**,**b** were revealed by GC-MS, and after a short purification were subjected to the next step.
(13) Minuti, L.; Taticchi, A.; Marrocchi, A. *Tetrahedron: Asymmetry*, **2000**, *10*, 4221−4225 and references cited therein.
(14) The signals of C-2′ and C-6′ carbons, for the adducts **6cx**,**ex**,**fx** and **6cy**,**dy**,**fy** and **10dy**,**ey** and **12** in the ^{13}C NMR spectra are absent. We observed the C-2′ and C-6′ signals in the HMBC experiment for the adduct **6ey.**

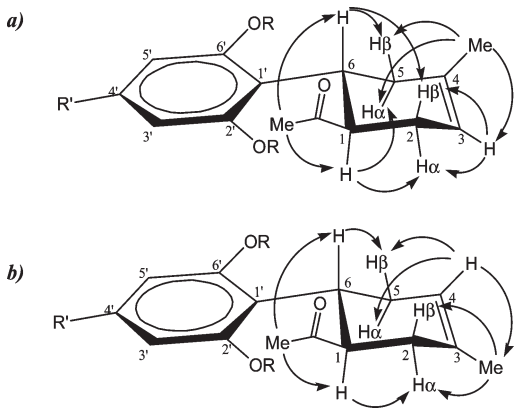


FIGURE 3. Structure assigned to (a) cycloadducts **6y** and (b) cycloadducts **10y**. The arrows indicate the observed 2D-NOESY correlation for cycloadducts: (a) **6ey** (R = Me, R′ = C_5H_{11}) and (b) **10dy** (R = MOM, R′ = C_5H_{11}).

measured for $^3J_{3,4}$. The trans-configuration of H-1 and H-6 protons for all adducts **6** and **10** was based on the relevant interproton coupling constant values ($^3J_{1,6}$ = 10.5−11.6 Hz), typical for a *trans*-pseudoaxial orientation. This configuration was further supported by 2D-NOESY experiments. The NOESY correlation peaks observed between H-1 and H-2α and H-5α, and between H-6 and H-2*β* and H-5*β*, together with the absence of a correlation peak between H-1 and H-6 confirmed the trans-relationship of H-1 and H-6 (Figure 3). The regiochemical assignment of the methyl group at C-4 in adducts **6y** (Figure 3a) and at C-3 in adducts **10y** is supported by the 2D-NOESY experiments performed on **6ey** and **10dy**, respectively (Figure 3). The presence of NOESY correlation peak was observed between H-3 and H-2α and H-2*β*, and between the 4-Me protons and H-5α and H-5*β* for adduct **6ey** (Figure 3a), while the NOESY correlation peak was observed between H-4 and H-5α, and H-5*β*, and between the 3-Me protons and H-2α and H-2*β* for adduct **10dy** (Figure 3b), thus indicating the assigned regiochemistry of the methyl group at C-4 and at C-3 for **6ey** and **10dy**, respectively. Finally, support for the structure depicted in Figure 3 for the adducts **6ay**−**dy**, **6fy**, and **10ey** was given by the great similarity of the proton and carbon shifts of comparable sites of the cyclohexene ring of these adducts with **6ey** and **10dy**, respectively.

The trans configurations of Δ^8-THCs **2** and **7a** were confirmed by comparing the NMR data with those of previously reported natural Δ^8-THC (**2**)[6a−d] and with those of our previous work.[4b]

Conclusions

In summary, a high-yielding method for constructing the 6,6-dimethyltetrahydro-6*H*-benzo[*c*]chromene skeleton **7** via Diels−Alder reactions of low reactive alkoxybenzylideneacetone derivatives **4** with methyl-1,3-butadienes **5** was developed. The cycloaddition reactions were activated by a combination of high pressure (8−11 kbar) and the mild Lewis acid $HfCl_4 \cdot 2THF$ or $AlCl_3 \cdot 2THF$ that are useful THF-complex salts which prevent the polymerization of the dienes **5** and allow these reactions to occur in high yield under mild reaction temperatures. Application to the synthesis of Δ^8-THC **2** and its analogue **7a** has been accomplished from selected Diels−Alder cycloadducts **6ey** and **6cy**, respectively, by Grignard addition, demethylation, and pyran ring formation. An easy and efficient resolution of cycloadduct **6ey** by the SAMP-hydrazone method provided a rapid synthesis of Δ^8-THC **2** in both enantiomeric pure forms.

Our proposed strategy to 6,6-dimethyltetrahydro-6*H*-benzo[*c*]chromene-based *privileged* structures **7** is a new synthetic route that may be applied to the synthesis of a variety of naturally occurring products (i.e Δ^8-THC family) for use in bioassays and SAR studies. Future applications of this methodology to the synthesis of other natural products will be reported.

Experimental Section

General Procedure for the Diels−Alder Reaction of Benzylideneacetones 4a−f with Dienes 5x,y. The catalyzed cycloaddition reactions of benzylideneacetones **4** with dienes **5** were accomplished (A) at normal pressure and (B) under 8−11 kbar pressure conditions. Details are listed in Tables 1 and 2.

Condition A. The catalyst (10−25 mol %) was added to a stirred solution of benzylideneacetone **4** (1.5 mmol) in 15 mL of dry toluene or CH_2Cl_2 and the mixture was left at room temperature for 30 min. Diene **5** (3 mol equiv) and a few crystals of hydroquinone were then added and the mixture was poured into an oil bath under magnetic stirring at the indicated reaction temperature and time. The cooled mixture was poured into a saturated $NaHCO_3$ solution (15 mL) and extracted twice with CH_2Cl_2.

The combined extracts were washed with saturated brine, dried (Na_2SO_4), and evaporated under vacuo. The crude mixture was purified by column chromatography on silica gel by using a 9:1 mixture of petroleum ether/diethyl ether as eluent to give cycloadducts **6**.

Condition B. A solution of benzylideneacetone **4** (1.5 mmol) in 10 mL of CH_2Cl_2 was placed in a 15 mL Teflon vial; the catalyst (10−25 mol %) was added and the mixture was left at room temperature for 30 min. Diene **5** (2−4 molar equiv) and a few crystals of hydroquinone were then added and the vial was filled with the solvent. The vial was closed and kept at 8−11 kbar at the indicated temperature for the appropriate time. After depressurizing, the mixture was worked up and purified as above giving pure cycloadducts **6**.

6ax: white solid, mp 75−76 °C (*n*-hexane); IR ($CHCl_3$) 1702 (C=O) cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 1.64 (s, 3H, CH_3), 1.68 (s, 3H, CH_3), 1.91 (s, 3H, CH_3C=O), 2.09 (dd broad, 1H, J = 16.7, 4.4 Hz, H-5*β*), 2.17 (d broad, 2H, J = 7.0 Hz, H-2α, H-2*β*), 2.28 (dd broad, 1H, J = 16.7, 11.3 Hz, H-5α), 3.16 (ddd, 1H, J = 10.8, 10.8, 5.3 Hz, H-1), 3.48 (ddd, 1H, J = 10.8, 8.5, 7.5 Hz, H-6), 3.84 (s, 3H, OCH_3), 6.85 (d, 1H, J = 8.2 Hz, H-3′), 6.89 (t, 1H, J = 7.5 Hz, H-5′), 7.11 (d, 1H, J = 7.5 Hz, H-6′), 7.16 (dd, 1H, J = 8.2, 7.5 Hz, H-4′); ^{13}C NMR (400 MHz, $CDCl_3$) δ 18.7 (2C), 28.1, 34.7, 36.6, 38.6, 52.7, 55.3, 110.7, 120.8, 123.6, 125.6, 127.3, 127.8, 132.2, 156.9, 212.2; MS (*m*/*e*) (rel intensity) 43 (45), 77 (18), 91 (66), 95 (27), 107 (36), 115 (18), 121 (98), 122 (35), 135 (32), 136 (17), 137 (95), 145 (100), 150 (43), 161 (46), 173 (17), 213 (22), 214 (23), 215 (66), 216 (21), 258 (M^+, 68). Anal. Calcd for $C_{17}H_{22}O_2$: C, 79.03; H, 8.58. Found: C, 79.17; H, 8.45.

6ay: oil; IR ($CHCl_3$) 1702 (C=O) cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 1.69 (s, 3H, 4-CH_3), 1.92 (s, 3H, CH_3C=O), 2.13−2.33 (m, 4H, H-2α, H-2*β*, H-5α, H-5*β*), 3.11 (ddd, 1H, J = 10.5, 10.5, 5.6 Hz, H-1), 3.53 (ddd, 1H, J = 10.5, 9.5, 6.5 Hz, H-6,), 3.84 (s, 3H, OCH_3), 5.46 (s broad, 1H, H-3), 6.86 (d, 1H, J = 8.2 Hz, H-3′), 6.90 (t, 1H, J = 7.5 Hz, H-5′), 7.12 (d, 1H, J = 7.5 Hz, H-6′), 7.17 (dd, 1H, J = 8.2, 7.5 Hz, H-4′); ^{13}C NMR (400 MHz, $CDCl_3$) δ 23.1, 28.2, 28.5, 36.2, 36.8, 51.6, 55.3, 110.7, 118.8, 120.9, 127.4, 127.9, 132.2, 134.0, 156.8, 212.3; MS (*m*/*e*) (rel

intensity) 43 (35), 77 (18), 91 (53), 93 (24), 108 (25), 115 (17), 121 (100), 122 (15), 145 (67), 146 (11), 159 (21), 161 (35), 186 (14), 201 (66), 202 (11), 244 (M^+, 62). Anal. Calcd for $C_{16}H_{20}O_2$: C, 78.65; H, 8.25. Found: C, 78.78; H, 8.31.

6bx: White solid, mp 64−65 °C (*n*-hexane); IR ($CHCl_3$) 1702 (C=O) cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 1.62 (s, 3H, CH_3), 1.66 (s, 3H, CH_3), 1.90 (s, 3H, CH_3C=O), 2.07 (dd broad, 1H, J = 16.7, 4.6 Hz, H-5β), 2.14 (d broad, 2H, J = 7.5 Hz, H-2α, H-2β), 2.27 (dd broad, 1H, J = 16.7, 10.6 Hz, H-5α), 3.11 (ddd, 1H, J = 10.9, 10.9, 5.3 Hz, H-1), 3.36 (ddd, 1H, J = 11.1, 8.1, 8.1 Hz, H-6), 3.77 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 6.42 (d, 1H, J = 7.2 Hz, H-5′), 6.43 (s, 1H, H-3′), 6.99 (d, 1H, J = 7.2 Hz, H-6′); ^{13}C NMR (400 MHz, $CDCl_3$) δ 18.6 (2C), 27.9, 34.7, 36.3, 38.8, 52.9, 55.2, 55.3, 98.7, 104.3, 123.5, 124.5, 125.7, 128.3, 157.8, 159.1, 212.3; MS (*m*/*e*) (rel intensity) 43 (14), 91 (13), 106 (11), 107 (28), 121 (17), 135 (12), 150 (40), 151 (86), 152 (12), 175 (100), 176 (18), 191 (56), 206 (17), 246 (12), 288 (M^+, 25). Anal. Calcd for $C_{18}H_{24}O_3$: C, 74.97; H, 8.39. Found: C, 74.86; H, 8.34.

6by: oil; IR ($CHCl_3$) 1702 (C=O) cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 1.68 (s, 3H, 4-CH_3), 1.91 (s, 3H, CH_3C=O), 2.10−2.33 (m, 4H, H-2α, H-2β, H-5α, H-5β), 3.06 (ddd, 1H, J = 10.4, 10.4, 5.5 Hz, H-1), 3.41 (ddd, 1H, J = 10.8, 7.5, 7.5 Hz, H-6), 3.78 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 5.44 (s broad, 1H, H-3), 6.43 (d, 1H, J = 6.9 Hz, H-5′), 6.44 (s, 1H, H-3′), 7.01 (d, 1H, J = 6.9 Hz, H-6′); ^{13}C NMR (400 MHz, $CDCl_3$) δ 23.1, 28.1, 28.6, 36.0, 37.1, 51.9, 55.2, 55.3, 98.8, 104.4, 118.8, 124.6, 128.5, 134.1, 157.9, 159.2, 212.6; MS *m*/*e* (rel intensity) 91 (30), 138 (100), 139 (28), 151 (53), 175 (71), 274 (M^+, 10). Anal. Calcd for $C_{17}H_{22}O_3$: C, 74.42; H, 8.08. Found: C, 74.59; H, 8.05.

6cx: white solid; mp 79−80 °C (*n*-hexane); IR ($CHCl_3$) 1701 (C=O) cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 1.46 (s, 3H, CH_3), 1.51 (s, 3H, CH_3), 1.71 (s, 3H, CH_3C=O), 1.76 (d broad, 1H, J = 16.4 Hz, H-5β), 1.87 (d broad, 1H, J = 16.3 Hz, H-2β), 2.09 (dd broad, 1H, J = 16.3, 10.8 Hz, H-2α), 2.37 (dd broad, 1H, J = 16.4, 11.5 Hz, H-5α), 3.45 (ddd, 1H, J = 11.6, 11.6, 4.8 Hz, H-1), 3.54 (ddd, 1H, J = 11.5, 11.5, 5.1 Hz, H-6), 3.63 (s, 6H, 2′-OCH_3, 6′-OCH_3), 6.35 (d, 2H, J = 8.3 Hz, H-3′, H-5′), 6.94 (t, 1H, J = 8.3 Hz, H-4′); ^{13}C NMR (400 MHz, $CDCl_3$) δ 18.7 (2C), 27.9, 33.7, 35.5, 36.1, 51.1, 55.6, 55.8, 104.3 (2C), 119.2, 123.6, 126.1, 127.5, 213.0; MS *m*/*e* (rel intensity) 43 (60), 91 (44), 107 (32), 138 (52), 150 (52), 151 (83), 152 (25), 175 (100), 176 (17), 191 (14), 288 (M^+, 2). Anal. Calcd for $C_{18}H_{24}O_3$: C, 74.97; H, 8.39. Found: C, 74.82; H, 8.35.

6cy: white solid, mp 33−34 °C (*n*-hexane); IR ($CHCl_3$) 1700 (C=O) cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 1.53 (s, 3H, 4-CH_3), 1.72 (s, 3H, CH_3C=O), 1.78 (dd broad, 1H, J = 17.2, 5.1 Hz, H-5β), 1.97−2.15 (m, 2H, H-2α, H-2β), 2.37(dd broad, 1H, J = 17.2, 11.6 Hz, H-5α), 3.41 (ddd, 1H, J = 11.3, 11.3, 5.5 Hz, H-1), 3.66 (ddd, 1H, J = 11.5, 11.5, 5.3 Hz, H-6), 3.65 (s, 6H, 2′-OCH_3, 6′-OCH_3), 5.29 (s broad, 1H, H-3), 6.37 (d, 2H, J = 8.3 Hz, H-3′, H-5′), 6.96 (t, 1H, J = 8.3 Hz, H-4′); ^{13}C NMR (400 MHz, $CDCl_3$) δ 23.2, 28.0, 29.4, 33.3, 34.5, 50.3, 55.9 (2C), 104.3 (2C), 118.8, 119.1, 127.6, 134.6, 213.2; MS *m*/*e* (rel intensity) 43 (20), 77 (13), 91 (28), 93 (16), 121 (13), 138 (100), 139 (17), 151 (61), 175 (86), 176 (15), 191 (15), 274 (M^+, 12). Anal. Calcd for $C_{17}H_{22}O_3$: C, 74.42; H, 8.08. Found: C, 74.56; H, 8.12.

10cy: MS *m*/*e* (rel intensity) 43 (12), 91 (18), 91 (28), 136 (19), 121 (13), 138 (56), 151 (46), 175 (100), 176 (16), 191 (13), 274 (M^+, 2).

6dx: oil; IR ($CHCl_3$) 1701 (C=O) cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 1.64 (s, 3H, CH_3), 1.69 (s, 3H, CH_3), 1.91 (s, 3H, CH_3C=O), 1.97 (dd broad, 1H, J = 17.2, 4.7 Hz, H-5β), 2.07 (dd broad, 1H, J = 16.7, 4.5 Hz, H-2β), 2.27 (dd broad, 1H, J = 16.7, 11.3 Hz, H-2α), 2.58 (dd broad, 1H, J = 17.2, 11.2 Hz, H-5α), 3.50 (s, 6H, $-OCH_3$, $-OCH_3$), 3.63 (ddd, 1H, J = 11.5, 11.5, 4.9 Hz, H-1), 3.75 (ddd, 1H, J = 11.5, 11.5, 5.3 Hz, H-6), 5.18 (s, 4H, 2′-OCH_2-, 6′-OCH_2-), 6.77 (d, 2H, J = 8.3 Hz, H-3′, H-5′), 7.06 (t, 1H, J = 8.3 Hz, H-4′); ^{13}C NMR (400 MHz, $CHCl_3$) δ 18.7 (2C), 27.9, 34.0, 35.6, 36.2, 51.3 (2C), 56.1, 94.6 (2C), 108.3 (2C), 120.6, 123.7, 126.0, 127.7, 156.7 (2C), 212.5; MS *m*/*e* (rel intensity) 43 (27), 45 (100), 107 (15), 123 (46), 147 (16), 149 (14), 150 (22), 198 (17), 215 (19), 227 (14), 229 (42), 241 (35), 253 (14), 271 (21), 286 (14), 303 (34), 348 (M^+, 3). Anal. Calcd for $C_{20}H_{28}O_5$: C, 68.94; H, 8.10. Found: C, 68.81; H, 8.06.

6dy: oil; IR ($CHCl_3$) 1702 (C=O) cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 1.69 (s, 3H, 4-CH_3), 1.90 (s, 3H, CH_3C=O), 1.97 (dd broad, 1H, J = 17.3, 5.3 Hz, H-5β), 2.22 (m, 2H, H-2α, H-2β), 2.55 (dd broad, 1H, J = 17.3, 11.4 Hz, H-5α), 3.51 (s, 6H, $-OCH_3$, $-OCH_3$), 3.57 (ddd, 1H, J = 10.8, 10.8, 6.1 Hz, H-1), 3.79 (ddd, 1H, J = 11.6, 11.6, 5.3 Hz, H-6), 5.19 (s, 4H, 2′-OCH_2-, 6′-OCH_2-), 5.47 (s broad, 1H, H-3), 6.77 (d, 2H, J = 8.3 Hz, H-3′, H-5′), 7.07 (t, 1H, J = 8.3 Hz, H-4′); ^{13}C NMR (400 MHz, $CDCl_3$) δ 23.2, 28.0, 29.5, 33.7, 34.7, 50.4, 56.1 (2C), 94.7 (2C), 108.3 (2C), 118.9, 120.6, 127.8, 134.5, 212.8; MS *m*/*e* (rel intensity) 43 (24), 45 (100), 123 (30), 135 (17), 147 (17), 198 (20), 201 (13), 215 (45), 227 (30), 239 (13), 257 (23), 289 (20), 334 (M^+, 4). Anal. Calcd for $C_{19}H_{26}O_5$: C, 68.24; H, 7.84. Found: C, 68.08; H, 7.88.

10dy: oil; ^1H NMR (400 MHz; C_6D_6) δ 1.71 (s, 3H, 3-CH_3), 1.88 (s, 3H, CH_3C=O), 2.00 (dd, 1H, J = 17.1, 4.1 Hz, H-2α), 2.24−2.40 (m, 1H, H-5β, H-2β), 2.90 (m, 1H, H-5α), 3.31 (s, 6H, $-OCH_3$, $-OCH_3$), 3.90 (ddd, 1H, J = 11.6, 11.6, 4.9 Hz, H-1), 4.13 (ddd, 1H, J = 11.6, 11.6, 5.1 Hz, H-6), 4.98 (s, 4H, 2′-OCH_2-, 6′-OCH_2-), 5.59 (s broad, 1H, H-4), 6.90−7.05 (m, 3H, H-3′, H-4′, H-5′); ^{13}C NMR (400 MHz, $CDCl_3$) δ 23.4, 28.1, 29.9, 33.3, 33.9, 50.7, 56.1, 94.7, 108.3, 120.5, 121.4, 127.8, 132.1, 212.5; MS *m*/*e* (rel intensity) 43 (15), 45 (100), 123 (9), 147 (10), 198 (16), 215 (12), 227 (12), 334 (1).

6ex: light yellow oil; IR ($CHCl_3$) 1703 (C=O) cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 0.9 (t, 3H, J = 6.6 Hz, CH_3-), 1.33 (m, 4H, $-CH_2CH_2-$), 1.59 (m, 2H, $-CH_2-$), 1.62 (s, 3H, CH_3), 1.66 (s, 3H, CH_3), 1.87 (s, 3H, CH_3C=O), 1.90 (d broad, 1H, J = 16.4 Hz, H-5β), 2.0 (d broad, 1H, J = 16.2 Hz, H-2β), 2.25 (dd broad, 1H, J = 16.2, 11.2 Hz, H-2α), 2.52 (t, 2H, J = 7.8 Hz, $-CH_2-$), 2.53 (m, 1H, H-5α), 3.61 (m, 2H, H-1, H-6), 3.78 (s, 6H, 2′-OCH_3, 6′-OCH_3), 6.33 (s, 2H, H-3′, H-5′); ^{13}C NMR (400 MHz, $CDCl_3$) δ 14.0, 18.7 (2C), 22.5, 27.9, 31.0, 31.6, 33.6, 35.5, 36.3, 36.4, 51.2, 55.5, 55.7, 104.5 (2C), 116.3, 123.6, 126.2, 142.7, 213.3; MS *m*/*e* (rel intensity) 43 (35), 91 (15), 107 (31), 150 (38), 152 (54), 208 (78), 209 (22), 221 (100), 245 (100), 358 (M^+, 17). Anal. Calcd for $C_{23}H_{34}O_3$: C, 77.05; H, 9.56. Found: C, 77.24; H, 9.48.

6ey: white solid; mp 39−41 °C (*n*-hexane); IR ($CHCl_3$) 1700 (C=O) cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 0.90 (t, 3H, J = 6.9 Hz, $-CH_3$), 1.28−140 (m, 4H, $-CH_2-CH_2-$), 1.60 (m, 2H, $-CH_2-$), 1.68 (s, 3H, 4-CH_3), 1.86 (s, 3H, CH_3C=O), 1.91 (dd broad, 1H, J = 17.8, 5.1 Hz, H-5β), 2.10−2.30 (m, 2H, H-2α, H-2β), 2.52 (m, 1H, H-5α), 2.53 (t, 2H, J = 7.8 Hz, $-CH_2-$), 3.55 (ddd, 1H, J = 11.2, 11.2, 5.3 Hz, H-1), 3.67 (ddd, 1H, J = 11.5, 11.5, 6.2 Hz, H-6), 3.80 (s, 6H, 2′-OCH_3, 6′-OCH_3), 5.43 (s broad, 1H, H-3), 6.34 (s, 2H, H-3′, H-5′); ^{13}C NMR (400 MHz, $CHCl_3$) δ 14.0 (C-5″), 22.5 (C-4″), 23.2 (4-CH_3), 28.0 (CH_3C=O), 29.4 (C-2), 31.0 (C-2″), 31.6 (C-3″), 33.2 (C-6), 34.8 (C-5), 36.4 (C-1″), 50.4 (C-1), 55.9 (2′-OCH_3, 6′-OCH_3), 104.5 (C-3′, C-5′), 116.3 (C-1′), 118.8 (C-3), 134.7 (C-4), 142.7 (C-4′), 158.5 (C-2′, C-6′), 213.5 (C=O); MS *m*/*e* (rel intensity)[15] 43 (12), 152 (32), 208 (42), 221 (30), 245 (100), 246 (18), 301 (8), 344 (M^+, 16). Anal. Calcd for $C_{22}H_{32}O_3$: C, 76.70; H, 9.36. Found: C, 76.81; H, 9.32.

10ey: oil; ^1H NMR (400 MHz; C_6D_6) δ 0.97 (t, 3H, J = 7.1 Hz, CH_3-), 1.37 (m, 4H, $-CH_2-CH_2-$), 1.63−1.77 (m, 2H, $-CH_2-$), 1.70 (s, 3H, 3-CH_3), 1.89 (s, 3H, CH_3C=O), 2.02 (dd, 1H, J = 17.1, 4.1 Hz, H-2α), 2.13−2.55 (m, 3H, H-5β, H-2β, H-2α), 2.59 (t, 2H, J = 7.7 Hz, $-CH_2-$), 2.92 (m, 1H, H-5α),

(15) Claussen, U.; Fehlhaber, H. W.; Korte, F. *Tetrahedron* **1966**, *22*, 3535–3543.

3.50 (s, 6H, 2′-OCH_3, 6′-OCH_3), 3.92 (ddd, 1H, J = 11.5, 11.5, 4.9 Hz, H-1), 4.13 (ddd, 1H, J = 11.5, 11.5, 5.1 Hz, H-6), 5.56 (s broad, 1H, H-4), 6.40 (s, 2H, H-3′ e H-5′); ^{13}C NMR (400 MHz, $CDCl_3$) δ 16.0, 20.7, 23.6, 28.1, 30.0, 30.8, 31.5, 32.9, 33.8, 35.5, 50.7, 55.7 (2C), 103.9 (2C), 108.4, 121.6, 132.0, 142.7; MS m/e (rel intensity) 43 (9), 152 (16), 208 (33), 221 (22), 245 (100), 246 (18), 261 (6), 344 (M^+, 6).

6fx: oil; IR ($CHCl_3$) 1701 (C=O) cm^{-1}; ^{1}H NMR (400 MHz; $CDCl_3$) δ 0.89 (t, 3H, J = 6.9 Hz, $-CH_3$), 1.32 (m, 4H, $-CH_2CH_2-$), 1.57 (m, 2H, $-CH_2-$), 1.63 (s, 3H, CH_3), 1.68 (s, 3H, CH_3), 1.90 (s, 3H, CH_3C=O), 1.95 (dd broad, 1H, J = 17.2, 4.5 Hz, H-5β), 2.05 (dd broad, 1H, J = 16.7, 4.7 Hz, H-2β), 2.27 (dd broad, 1H, J = 16.7, 11.4 Hz, H-2α), 2.50 (t, 2H, J = 7.9 Hz, $-CH_2$), 2.57 (dd broad, 1H, J = 17.2, 11.2 Hz, H-5α), 3.50 (s, 6H, 2′-OCH_3, 6′-OCH_3), 3.60 (ddd, 1H, J = 11.4, 11.4, 4.9 Hz, H-1), 3.67 (ddd, 1H, J = 11.4, 11.4, 6.2 Hz, H-6), 5.17 (s, 4H, 2′-OCH_2, 6′-OCH_2), 6.60 (s, 2H, H-3′, H-5′); ^{13}C NMR (400 MHz, $CDCl_3$) δ 14.0, 18.7 (2C), 22.5, 27.9, 30.9, 31.6, 34.0, 35.6, 36.2, 36.4, 51.4, 56.1 (2C), 94.8 (2C), 108.5 (2C), 117.7, 123.7, 126.1, 143.1, 213.0; MS m/e (rel intensity) 43 (26), 45 (100), 107 (17), 119 (13), 123 (27), 149 (12), 150 (19), 193 (40), 217 (13), 268 (53), 269 (13), 275 (40), 281 (22), 285 (12), 299 (35), 356 (13), 373 (45), 418 (M^+, 3). Anal. Calcd for $C_{25}H_{38}O_5$: C, 71.74; H, 9.15. Found: C, 71.62; H, 9.12.

6fy: oil; IR ($CHCl_3$) 1701 (C=O) cm^{-1}; ^{1}H NMR (400 MHz; $CDCl_3$) δ 0.89 (t, 3H, J = 6.9 Hz, CH_3-), 1.31 (m, 4H, $-CH_2-CH_2-$), 1.57 (m, 2H, $-CH_2-$), 1.69 (s, 3H, 4-CH_3), 1.90 (s, 3H, CH_3C=O), 1.96 (dd, 1H, J = 17.1, 5.0 Hz, H-5β), 2.13−2.30 (m, 2H, H-2α, H-2$_\beta$), 2.50 (t, 2H, J = 7.8 Hz, $-CH_2-$), 2.55 (dd broad, 1H, J = 17.1, 11.2 Hz, H-5α), 3.51 (s, 6H, 2′-OCH_3, 6′-OCH_3), 3.54 (ddd, 1H, J = 11.0, 11.0, 5.6 Hz, H-1), 3.73 (ddd, 1H, J = 11.6, 11.6, 5.3 Hz, H-6), 5.18 (s, 4H, 2′-OCH_2-, 6′-OCH_2-), 5.46 (s broad, 1H, H-3), 6.60 (s, 2H, H-3′, H-5′); ^{13}C NMR (400 MHz, $CDCl_3$) δ 14.0, 22.5, 23.3, 28.0, 29.5, 30.9, 31.6, 33.9, 34.9, 36.2, 50.5, 56.1 (2C), 94.4 (2C), 108.5 (2C), 117.7, 118.9, 134.6, 143.2, 213.1; MS m/e (rel intensity) 43 (26), 45 (100), 109 (19), 193 (43), 217 (13), 225 (14), 231 (11), 268 (39), 269 (13), 275 (37), 285 (42), 295(10), 297 (31), 309 (10), 327 (30), 342 (12), 359 (17), 404 (M^+, 10). Anal. Calcd for $C_{24}H_{36}O_5$: C, 71.26; H, 8.97. Found: C, 71.34; H, 9.03.

10fy: MS m/e (rel intensity) 43 (21), 45 (80), 193 (30), 217 (24), 268 (100), 269 (23), 275 (88), 281 (22), 285 (39), 297 (34), 327 (24), 404 (M^+, 16).

General Procedure for Preparing Alcohols 11a,b and 13a,b.[3i] To a solution of cycloadduct **6** (0.274 mmol) in toluene (18.5 mL) was slowly added a 3.0 M solution of CH_3MgBr in ether (0.91 mL, 2.74 mmol) at room temperature. The mixture was heated at 60 °C for 1.5 h and then cooled to room temperature. The reaction was quenched with saturated NH_4Cl solution, poured into brine, and extracted with ether. The combined organic layers were dried over Na_2SO_4 and concentrated to give the desired alcohols **11** and **13** (98% yield).

11a: oil; IR ($CHCl_3$) 3690 (OH) cm^{-1}; H NMR (400 MHz; $CDCl_3$) δ 1.06 (s, 3H, CH_3C-OH), 1.07 (s, 3H, CH_3C-OH), 1.66 (s, 3H, 4-CH_3), 1.85 (dd broad, 1H, J = 18.2, 4.9 Hz, H-5β), 1.91 (dd broad, 1H, J = 17.2, 11.1 Hz, H-2β), 2.23 (d broad, 1H, J = 17.2 Hz, H-2α), 2.59 (ddd, 1H, J = 11.2, 11.2, 5.2 Hz, H-6), 2.70 (dd broad, 1H, J = 18.2, 10.2 Hz, H-5α), 3.48 (s, 3H, $-OCH_3$), 3.51 (ddd, 1H, J = 11.2, 11.2, 4.5 Hz, H-6), 3.52 (s, 3H, $-OCH_3$), 5.20 (AB system, 2H, $-OCH_2-$), 5.21 (AB system, 2H, $-OCH_2-$), 5.43 (s broad, 1H, H-3), 6.81 (m, 2H, H-3′, H-5′), 7.10 (t, 1H, J = 8.3 Hz, H-4′); ^{13}C NMR (400 MHz, $CDCl_3$) δ 22.9, 25.0, 28.8, 29.2, 33.0, 36.2, 45.1, 56.2, 56.3, 74.1, 94.5, 95.0, 108.4, 108.6, 120.1, 123.0, 127.8, 133.9, 154.9, 157.5. Anal. Calcd for $C_{20}H_{30}O_5$: C, 68.54; H, 8.36. Found: C, 68.28; H, 8.32.

11b: oil; IR ($CHCl_3$) 3690 (OH) cm^{-1}; ^{1}H NMR (400 MHz; $CDCl_3$) δ 0.89 (t, 3H, J = 7.0 Hz, $-CH_3$), 1.05 (s, 3H, CH_3C-OH), 1.07 (s, 3H, CH_3C-OH), 1.31 (m, 4H, $-CH_2CH_2-$), 1.57 (m, 2H, $-CH_2-$), 1.65 (s, 3H, 4-CH_3), 1.83 (dd broad, 1H, J = 17.5, 4.3 Hz, H-5β), 1.89 (m, 1H, H-2β), 2.21 (d broad, 1H, J = 17.1 Hz, H-2α), 2.51 (t, 2H, J = 7.7 Hz, $-CH_2-$), 2.56 (ddd, 1H, J = 11.2, 11.2, 5.2 Hz, H-6), 2.69 (dd broad, 1H, J = 17.5, 10.4 Hz, H-5α), 3.44 (ddd, 1H, J = 11.3, 11.3, 5.9 Hz, H-6), 3.47 (s, 3H, $-OCH_3$), 3.51 (s, 3H, $-OCH_3$), 5.18 (AB system, 2H, $-OCH_2-$), 5.19 (AB system, 2H, $-OCH_2-$), 5.41 (s broad, 1H, H-3), 6.62 (s, 1H, H-3′or H-5′), 6.63 (s, 2H, H-3′ or H-5′); ^{13}C NMR (400 MHz, $CDCl_3$) δ 14.1, 22.5, 22.9, 24.9, 28.9, 29.3, 31.0, 31.6, 32.8, 36.2, 36.4, 45.1, 56.2, 56.3, 74.2, 94.5, 95.1, 108.6, 108.7, 119.8, 120.1, 134.0, 143.4, 154.7, 157.2. Anal. Calcd for $C_{25}H_{40}O_5$: C, 71.39; H, 9.59. Found: C, 71.47; H, 9.52.

13a: oil; MS (m/e) (rel intensity) 43 (17), 134 (128), 193 (24), 231 (30), 257 (37), 271 (21), 275 (52), 281 (100), 283 (33), 289 (87), 290 (M^+, 19).

13b: oil; IR ($CHCl_3$) 3690.1 (OH) cm^{-1}; ^{1}H NMR (400 MHz; $CDCl_3$) δ 0.75 (t, 3H, J = 7.1 Hz, $-CH_3$), 0.87 (s, 3H, CH_3C-OH), 0.88 (s, 3H, CH_3C-OH), 1.18 (m, 4H, $-CH_2CH_2-$), 1.40−1.55 (m, 2H, $-CH_2-$), 1.48 (s, 3H, 4-CH_3), 1.62 (dd broad, 1H, J = 17.3, 4.4 Hz, H-5β), 1.72 (m, 1H, H-2β), 2.03 (d broad, 1H, J = 17.3 Hz, H-2α), 2.37 (ddd, 1H, J = 11.3, 11.3, 5.3 Hz, H-1), 2.39 (t, 2H, J = 7.5 Hz, $-CH_2-$), 2.51 (dd broad, 1H, J = 17.3, 11.4 Hz, H-5α), 3.27 (ddd, 1H, J = 11.4, 11.4, 5.2 Hz, H-6), 3.64 (s, 6H, 2′-OCH_3, 6′-OCH_3), 5.24 (s broad, 1H, H-3), 6.20 (s, 1H, H-3′), 6.23 (s, 1H, H-5′); ^{13}C NMR (400 MHz, $CDCl_3$) δ 14.0, 22.5, 22.8, 24.8, 28.8, 29.3, 31.0, 31.6, 32.3, 36.2, 36.4, 45.1, 55.2, 55.7, 74.1, 104.5, 104.9, 118.5, 120.0, 134.0, 142.9, 156.7, 159.2; MS m/e (rel intensity) 43 (9), 91 (7), 152 (8), 178 (9), 221 (100), 222 (16), 234 (19), 235 (10), 274 (13), 277 (44), 287 (11), 292 (11), 299 (20), 342 (22), 360 (M^+, 7). Anal. Calcd for $C_{23}H_{36}O_3$: C, 76.62; H, 10.06. Found: C, 76.79; H, 9.98.

12:[16] $SOCl_2$ (6 drops) was added to an ice-cold solution of alcohol **11a** (78.4 mg, 0.224 mmol) in 2.09 mL of dry pyridine. After 15 min, the solution was allowed to warm to rt, then diluted with brine and extracted twice with ether and twice with ethyl acetate. The extract was washed twice with HCl 0.1 M and several times with water until neutral, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel chromatography, eluting with petroleum ether/diethyl ether (7:3) to give **12** (75% yield) as an oil. ^{1}H NMR (400 MHz; $CDCl_3$) δ 1.53 (s, 3H, CH_3), 1.69 (s, 3H, 3′-CH_3), 1.95 (dd broad, 1H, J = 17.2, 4.6 Hz, H-2′β), 2.05 (d broad, 1H, J = 17.1 Hz, H-5′β), 2.18 (m, 1H, H-5′α), 2.60 (dd broad, 1H, J = 17.2, 10.8 Hz, H-2′α), 3.19 (ddd, 1H, J = 11.4, 11.4, 5.1 Hz, H-6′), 3.49 (s, 6H, 1-OCH_3, 3-OCH_3), 3.62 (ddd, 1H, J = 11.5, 11.5, 5.2 Hz, H-1′), 4.48 (s broad, 1H, H-1″), 4.61 (s broad, 1H, H-1″), 5.17 (m, 4H, 1-OCH_2-, 3-OCH_2-), 5.48 (s broad, 1H, H-4′), 6.77 (m, 2H, H-4, H-6), 7.05 (t, 1H, J = 8.3 Hz, H-5); ^{13}C NMR (400 MHz, $CDCl_3$) δ 18.4, 23.3, 32.5, 34.9, 35.5, 44.5, 56.0 (2C), 94.7, 95.0, 108.0, 108.2, 110.3, 120.7, 122.0, 127.1, 134.3, 148.9; MS m/e (rel intensity) 45 (100), 123 (11), 147 (12), 161 (17), 173 (10), 175 (12), 187 (25), 205 (24), 211 (16), 213 (23), 219 (37), 255 (22), 287 (42), 332 (M^+, 5). Anal. Calcd for $C_{20}H_{28}O_4$: C, 72.26; H, 8.49. Found: C, 72.39; H, 8.42.

Procedure for Preparing Δ^8-*trans*-THCs 2 and 7a. According to the procedure described by Trost et al.[5b] for synthesis of Δ^9-THC, starting from alcohol **13a**,**b** (0.2 mmol) and NaSMe (0.6 equiv) dissolved in DMF (2 mL), after stirring at 140 °C for 3 h diols **14a** and **14b** were obtained in 94% and 90% yields, respectively. Then, formation of the cyclized ethers **15a** and **15b** (80% and 78% yields, respectively) was achieved by treating a solution of **14a**,**b** (0.18 mmol) in CH_2Cl_2 (7 mL) with $ZnBr_2$ (0.35 mmol) and $MgSO_4$ (150 mg) at rt for 12 h. Finally, a solution of ethers **15a**,**b** (0.13 mmol) and NaSMe (1.3 mmol) in DMF (10 mL) was stirred

(16) Handrick, G. R.; Razdan, R. K.; Uliss, D. B.; Dalzell, H. C.; Boger, E. *J. Org. Chem.* **1977**, *42* (15), 2563–2568.

at 140 °C for 10 h to afford the desidered racemic Δ^8-THC (**2**) and the analogue **7a** in 66% and 68% yields, respectively.

14a: oil; MS *m*/*e* (rel intensity) 43 (10), 59 (11), 77 (13), 91 (11), 107 (18), 124 (11), 135 (15), 137 (46), 150 (14), 175 (100), 176 (13), 187 (10), 190 (19), 215 (83), 216 (13), 243 (11), 258 (63), 259 (12), 276 (M^+, 17).

14b: pale-yellow oil; IR ($CHCl_3$) 3689.9 (OH) cm^{-1}; MS *m*/*e* (rel intensity) 207 (38), 245 (100), 246 (21), 260 (14), 272 (15), 273 (12), 285 (37), 286 (10), 328 (32), 346 (M^+, 17).

15a: pale-yellow oil; MS *m*/*e* (rel intensity) 91 (10), 137 (18), 160 (12), 175 (100), 176 (13), 190 (19), 215 (60), 216 (11), 258 (M^+, 67).

15b: purified by silica gel chromatography, eluting with 97:3 petroleum ether/diethyl ether; colorless oil; ^{1}H NMR (400 MHz; $CDCl_3$) δ 0.73 (t, 3H, J = 6.9 Hz,-CH_3), 0.92 (s, 3H, 6-CH_3), 1.16 (m, 4H, $-CH_2-CH_2-$), 1.21 (s, 3H, 6-CH_3), 1.42 (m, 2H, $-CH_2-$), 1.53 (s, 3H, 9-CH_3), 1.58−1.73 (m, 3H, H-7α, H-7*β*, H-10α), 1.93−2.02 (m, 1H, H-10*β*), 2.34 (t, 2H, J = 8. 2 Hz, $-CH_2-$), 2.49 (ddd, 1H, J = 11.2, 11.0, 4.7 Hz, H-6a), 2.99 (dd broad, 1H, J = 16.8, 3.7 Hz, H-10a), 3.64 (s, 3H, OCH_3), 5.25 (s, 1H, H-8), 6.09 (s, 1H, H-2), 6.15 (s, 1H, H-4); ^{13}C NMR (400 MHz, $CDCl_3$) δ 14.0, 18.4, 22.6, 23.5, 27.6, 28.0, 30.8, 31.6, 31.8, 36.0, 36.2, 45.1, 55.1, 76.4, 103.0, 110.2, 111.9, 119.2, 135.0, 142.5, 154.3, 158.9; MS *m*/*e* (rel intensity) 43 (7), 91 (7), 174 (7), 188 (10), 207 (30), 215 (12), 245 (100), 272 (46), 273 (21), 285 (42), 286 (15), 328 (M^+, 97). Anal. Calcd for $C_{22}H_{32}O_2$: C, 80.44; H, 9.82. Found: C, 80.57; H, 9.76.

Δ^8-*trans*-THC (2): purified by silica gel chromatography, eluting with 95:5 petroleum ether/diethyl ether; colorless oil; IR ($CHCl_3$) 3597.6 (OH) cm^{-1}; ^{1}H NMR (400 MHz; $CDCl_3$) δ 0.73 (t, 3H, J = 7.1 Hz, $-CH_3$), 0.95 (s, 3H, 6-CH_3), 1.10−1.20 (m, 4H, $-CH_2-CH_2-$), 1.22 (s, 3H, 6-CH_3), 1.38 (m, 2H, $-CH_2-$), 1.54 (s, 3H, 9-CH_3), 1.60−1.75 (m, 3H, H-10α, H-7*β*, H-7α), 1.99 (m, 1H, H-10*β*), 2.28 (m, 2H, $-CH_2-$), 2.54 (ddd, 1H, J = 10.8, 10.8, 4.7 Hz, H-6a), 3.04 (dd, 1H, J = 16.2, 4.6 Hz, H-10a), 4.68 (s, 1H, OH), 5.27 (s, 1H, H-8), 5.94 (s, 1H, H-2), 6.12 (s, 1H, H-4); ^{13}C NMR (400 MHz, $CDCl_3$) δ 14.0, 18.5, 22.5, 23.5, 27.5, 27.9, 30.6, 31.3, 31.5, 35.4, 36.0, 44.9, 76.7, 107.6, 110.1, 110.5, 119.3, 134.7, 142.7, 154.7, 154.8; MS *m*/*e* (rel intensity) 119 (6), 174 (13), 193 (20), 201 (12), 231 (100), 232 (19), 246 (16), 258 (41), 259 (15), 271 (36), 272 (14), 314 (M^+, 72). Anal. Calcd for $C_{21}H_{30}O_2$: C, 80.21; H, 9.62. Found: C, 80.33; H, 9.54.

7a: purified by silica gel chromatography, eluting with 95:5 petroleum ether/diethyl ether; colorless oil; ^{1}H NMR (400 MHz; $CDCl_3$) δ 0.95 (s, 3H, 6-CH_3), 1.23 (s, 3H, 6-CH_3), 1.55 (s, 3H, 9-CH_3), 1.60−1.75 (m, 3H, H-10α, H-7*β*, H-7α), 1.99 (m,1H, H-10*β*), 2.57 (ddd, 1H, J = 11.1, 11.1, 4.7 Hz, H-6a), 3.06 (dd, 1H, J = 16.4, 4.3 Hz, H-10a), 4.63 (s, 1H, OH), 5.28 (s, 1H, H-8), 6.10 (d, 1H, J = 8.0 Hz, H-2), 6.27 (d, 1H, J = 8.0 Hz, H-4), 6.78 (t, 1H, J = 8.0 Hz, H-3); ^{13}C NMR (400 MHz, $CDCl_3$) δ 18.4, 23.5, 27.5, 27.9, 31.7, 35.9, 44.9, 76.7, 107.2, 110.4, 113.3, 119.3, 127.3, 134.7, 155.0, 152.2; MS *m*/*e* (rel intensity) 77 (13), 91 (13), 107 (12), 115 (12), 123 (23), 147 (12), 161 (100), 162 (20), 165 (10), 173 (12), 175 (15), 176 (35), 187 (12), 201 (100), 202 (19), 229 (21), 244 (M^+, 100). Anal. Calcd for $C_{16}H_{20}O_2$: C, 78.65; H, 8.25. Found: C, 78.81; H, 8.32.

SAMP-Hydrazones (*S*,*R*,*R*)-(+)-17 and (*S*,*S*,*S*)-(+)-17.[13] A few crystals of *p*-TsOH were added to a solution of *rac*-**6ey** (0.145 g, 0.42 mmol) and SAMP [*S*-(−)-**16**] (0.12 mL, 0.86 mmol) in 0.9 mL of heptane and then heated at 100 °C for 47 h. After cooling at room temperature, the reaction was diluted with Et_2O, washed with saturated aq $NaHCO_3$, and dried (Na_2SO_4). Evaporation of the solvent under vacuum gave a 1:1 mixture of two diastereoisomeric hydrazones **17**, which was chromatographed on silica gel (9:1 petroleum ether/diethyl ether) to give diastereomerically pure (*S*,*S*,*S*)-(+)-**17** and (*S*,*R*,*R*)-(+)-**17** in 40% and 37% yields, respectively.

(*S*,*R*,*R*)-(+)-17: pale-yellow oil; $[\alpha]_D$ +73 (*c* 1.99, $CHCl_3$); IR ($CHCl_3$) 1608 (C=N) cm^{-1}; ^{1}H NMR (400 MHz; $CDCl_3$) δ 0.73 (t, 3H, J = 6.9 Hz, $-CH_3$), 1.10−1.24 (m, 4H, $-CH_2CH_2-$), 1.33−1.60 (m, 5H, $-CH_2-$, H-4″, H-3″), 1.46 (s, 3H, $CH_3-C=N$), 1.50 (s, 3H, 4-CH_3), 1.66−1.76 (m, 2H, H-5*β*, H-3″), 1.87 (d broad, 1H, J = 16.8 Hz, H-2α), 1.99−2.14 (m, 2H, H-2*β*, H-5″), 2.34 (t, 2H, J = 7.8 Hz, $-CH_2-$), 2.49 (m, 1H, H-5α), 2.56 (dd, 1H, J = 9.5, 6.9 Hz, $-OCH_2-$), 2.73−2.78 (m, 2H, H-2″, H-5″), 2.84 (dd, 1H, J = 9.5, 3.5 Hz, $-OCH_2-$), 3.00 (s, 3H, $-OCH_3$), 3.20 (ddd, 1H, J = 11.5, 11.5, 5.1 Hz, H-1), 3.47 (ddd, 1H, J = 11.5, 11.5, 5.2 Hz, H-6), 3.59 (s, 3H, 2′-OCH_3), 3.64 (s, 3H, 6′-OCH_3), 5.25 (s broad, 1H, H-3), 6.14 (s, 1H, H-3′), 6.16 (s, 1H, H-5′); ^{13}C NMR (400 MHz, $CDCl_3$) δ 13.7, 14.0, 21.9, 22.5, 23.4, 26.3, 30.7, 31.1, 31.7, 33.6, 34.6, 36.5, 45.2, 53.4, 55.1, 55.8, 58.9, 66.1, 74.5, 103.8, 104.6, 116.8, 119.4, 134.5, 142.2, 157.4, 159.4, 170.6; MS *m*/*e* (rel intensity) 43 (6), 73 (9), 91 (6), 105 (6), 137 (27), 173 (6), 207 (13), 221 (43), 300 (20), 301 (16), 411 (100), 412 (30), 456 (M^+, 31). Anal. Calcd for $C_{28}H_{44}N_2O_3$: C, 73.64; H, 9.71; N, 6.13. Found: C, 73.51; H, 9.65; N, 6.06.

(*S*,*S*,*S*)-(+)-17: pale-yellow oil; $[\alpha]_D$ +115 (*c* 1.28, $CHCl_3$); IR ($CHCl_3$) 1607 (C=N) cm^{-1}; ^{1}H NMR (400 MHz; $CDCl_3$) δ 0.79 (t, 3H, J = 7.1 Hz, $-CH_3-$), 1.14−1.29 (m, 4H, $-CH_2CH_2-$), 1.38−1.55 (m, 6H, $-CH_2-$, H-4″, H-3″, H-5″), 1.49 (s, 3H, $CH_3-C=N$), 1.57 (s, 3H, 4-CH_3), 1.74−1.85 (m, 2H, H-5*β*, H-3″), 1.99 (d broad, 1H, J = 16.6 Hz, H-2α), 2.09 (dd broad, 1H, J = 16.6, 11.4 Hz, H-2*β*), 2.41 (t, 2H, J = 7.7 Hz, $-CH_2-$), 2.44 (m, 1H, H-5″), 2.52 (m, 1H, H-5α), 2.90−2.98 (m, 2H, H-2″, $-OCH_2-$), 3.17 (s, 3H, $-OCH_3$), 3.14−3.21 (m, 1H, $-OCH_2-$), 3.27 (ddd, 1H, J = 11.4, 11.4, 5.0 Hz, H-1), 3.50 (ddd, 1H, J = 11.5, 11.5, 5.1 Hz, H-6), 3.67 (s, 6H, 2′-OCH_3, 6′-OCH_3), 5.33 (s, 1H, H-3), 6.19 (s, 2H, H-3′, H-5′); ^{13}C NMR (400 MHz, $CDCl_3$) δ 14.0 (2C), 22.0, 22.5, 23.3, 26.7, 30.3, 31.3, 31.5, 33.7, 34.8, 36.4, 44.9, 53.6, 55.3, 55.8, 59.0, 66.1, 75.4, 103.8, 104.6, 116.9, 119.5, 134.5,142.2, 157.5, 159.5, 168.8; MS *m*/*e* (rel intensity) 43 (4), 70 (7), 105 (10), 144 (34), 221 (91), 222 (15), 301 (10), 310 (10), 342 (33), 343 (11), 411 (100), 412 (41), 456 (M^+, 22). Anal. Calcd for $C_{28}H_{44}N_2O_3$: C, 73.64; H, 9.71; N, 6.13. Found: C, 73.48; H, 9.62; N, 6.08.

Hydrolysis of the SAMP-Hydrazones (*S*,*R*,*R*)-(+)-17 and (*S*,*S*,*S*)-(+)-17[13] **and Synthesis of (*R*,*R*)-(−)- and (*S*,*S*)-(+)-Δ^8-THCs (2).** An aqueous saturated solution of oxalic acid (0.6 mL) was added to a solution of (*S*,*R*,*R*)-(+)-**17** (0.124 g, 0.27 mmol) in diethyl ether (3.96 mL). The resulting mixture was vigorously stirred for 4 days at room temperature. Then, the reaction mixture was diluted with Et_2O, washed with saturated aq $NaHCO_3$, and dried (Na_2SO_4). Evaporation of the solvent under vacuum gave a residue that was purified by column chromatography over silica gel. Elution with 9:1 petroleum ether/diethyl ether afforded 93 mg (75%) of pure (*R*,*R*)-(−)-**6ey**; $[\alpha]_D$ −23 (*c* 1.34, $CHCl_3$).

By using the procedure described above, hydrolysis of (*S*,*S*,*S*)-(+)-**17** (0.102 g, 0.22 mmol) gave pure ketone (*S*,*S*)-(+)-**6ey** in 65% yield; $[\alpha]_D$ +22 (*c* 0.6, $CHCl_3$).

The procedure described for the synthesis of racemic Δ^8-THC **2** (vide supra) was repeated with enantiomerical pure cyloadducts (*R*,*R*)-(−)-**6ey** and (*S*,*S*)-(+)-**6ey** to afford the (*R*,*R*)-(−)-Δ^8-THC **2** ($[\alpha]_D$ −245 (*c* 0.78, $CHCl_3$)) and (*S*,*S*)-(+)-Δ^8-THC **2** ($[\alpha]_D$ +240 (*c* 0.94, $CHCl_3$)), respectively, through the intermediates (*R*,*R*)-(−)-**13b** ($[\alpha]_D$ −13 (*c* 1.28, $CHCl_3$)) and (*S*,*S*)-(+)-**13b** ($[\alpha]_D$ +15 (*c* 0.78, $CHCl_3$)), and (*R*,*R*)-(−)-**15b** ($[\alpha]_D$ −178 (*c* 0.65, $CHCl_3$)) and (*S*,*S*)-(+)-**15b** ($[\alpha]_D$ +178 (*c* 0.545, $CHCl_3$)).

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