JOC The Journal of Organic Chemistry

ARTICLE

pubs.acs.org/joc

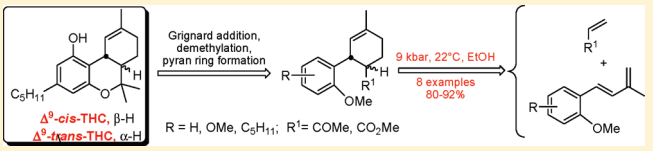
High-Pressure Access to the Δ^9-*cis*- and Δ^9-*trans*-Tetrahydrocannabinols Family

Lucio Minuti* and Eleonora Ballerini

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

Supporting Information

ABSTRACT: Diels–Alder reactions of a range of 1-(alkoxy/alkyl-substituted phenyl)buta-1,3-dienes with methyl vinyl ketone and methyl acrylate carried out in ethanol as the reaction medium under 9 kbar pressure were investigated. The use of high pressure as the activating method of the Diels–Alder reactions allows the efficient and endodiastereoselective generation of a series of *cis*-cyclohexenyl-benzene cycloadducts, which are selectively converted into their *trans*-epimers. The *cis*-cyclohexenyl-benzenes and *trans*-cyclohexenyl-benzenes produced are useful precursors for accessing substituted privileged *cis*-6a,7,8,10a-tetrahydro-6*H*-benzo[*c*]chromene and *trans*-6a,7,8,10a-tetrahydro-6*H*-benzo[*c*]chromene skeletons. The total syntheses of Δ^9-*cis*-tetrahydrocannabinol (THC) and Δ^9-*trans*-THC, through the use of selected Diels–Alder adducts, are described. Finally, a route for obtaining Δ^9-*trans*-THC in both enantiomeric pure forms based on the (*S*)-(−)-1-amino-2-(methoxymethyl)pyrrolidine (SAMP)-hydrazone method is also reported.



INTRODUCTION

In recent years, our interest has been focused on developing novel environmentally friendly synthetic routes to target molecules incorporating the tetrahydro-6*H*-benzo[*c*]chromene system.[1] This structural motif has been proposed as a privileged structure[2] as it occurs in a diverse range of bioactive natural products and can interact with a variety of cellular targets. The cannabinoids are examples of natural products with this privileged structural unit (e.g., Δ^9-*trans*-THC **2** and Δ^8-*trans*-THC **4**) (Figure 1), which represent a group of C_{21} terpenophenolic compounds found in *Cannabis sativa* var. *indica*.[3] The phytocannabinoids Δ^8-THC and Δ^9-THC have comparable potencies and act upon two cellular receptors, the central cannabinoid receptor, CB_1,[3a] which is found mainly in the brain, and the peripheral cannabinoid receptor, CB_2,[3c] which is found almost exclusively in the immune system.[4] Synthetic cannabinoids that selectively interact with only one receptor are highly desired, especially since CB_2-selective ligands should limit the side-effects associated with CB1 receptor activation.[5] Thus, extensive structure–activity relationship (SAR) studies of cannabinoid analogues with affinities for the CB_1 and CB_2 receptors have been reported,[6] which has highlighted the need to develop short, flexible, and efficient synthetic routes to easily obtain a large number of target compounds in a stereochemically pure form.

Several strategies for constructing the Δ^8-THC and Δ^9-THC derivatives have primarily focused on the condensation of a relevant aromatic ring system with an appropriately functionalized achiral or chiral monoterpene, followed by pyran formation.[7] Most of them suffer from serious drawbacks, such as harsh reaction conditions and little control of the *cis*-*trans* stereochemistry at the cyclohexene ring junction and of the position of the double bond (i.e., the Δ^8 isomer is thermodynamically more stable than the Δ^9 isomer). This has lowered the yields and limited the flexibility of the reactions, and thus the possibility of constructing libraries of cannabinoid analogues and other new natural product-like compounds. Although the Diels–Alder reaction represents an efficient tool for the stereocontrolled synthesis of functionalized polycyclic compounds, there are only a few synthetic approaches to cannabinoids in the literature that are based on the Diels–Alder reaction.[8]

Recently, our laboratory reported a high-yielding and environmentally safe method for the construction of the *cis*-6a,7,10,10a-tetrahydro-6*H*-benzo[*c*]chromene and *trans*-6a,7,10,10a-tetrahydro-6*H*-benzo[*c*]chromene skeleton through the use of a Diels–Alder reaction using coumarins[1b,d] or alkoxybenzylideneacetones[1e] as dienophiles. Due to the low reactivity of the coumarins and the benzylideneacetones double bond as dienophiles, we observed previously that they react with 1,3-butadienes at normal pressure only at high temperature and over long reaction times, to give their relative cycloadducts in low yields. Thus, we reported on our investigations into the great utility of high pressure (9–11 kbar) as an activating method in the Diels–Alder strategy to access *cis*- and *trans*-polysubstituted benzo[*c*]-chromene templates in high yields and under milder reaction conditions.[9] For example, by using hydroxy-substituted 3-cyanocoumarins as dienophiles, we developed a Diels–Alder strategy for synthesizing a range of hydroxy-substituted *cis*-6a,7,10,10a-6a-cyano-benzo[*c*]chromenones and applied this to the synthesis of Δ^6-3,4-*cis*-cannabidiol and Δ^8-*cis*-THC (**3**), in order to open a route to the non-natural Δ^8-*cis*-THCs family.[1b] Instead, when we used alkoxy-benzylideneacetones as dienophiles, we exploited this

Received: April 18, 2011
Published: May 12, 2011

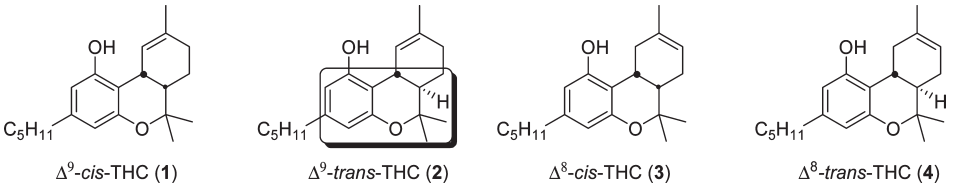
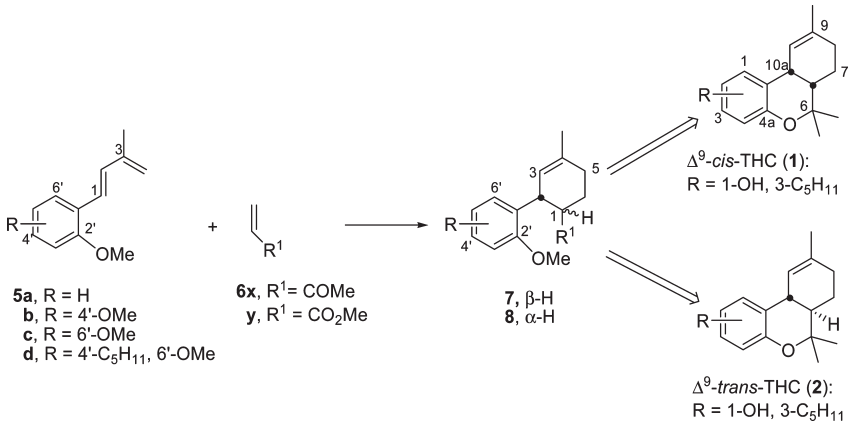


Figure 1. Tetrahydrocannabinol (THC) family.

Scheme 1. Proposed Synthesis of the Δ^9-*cis*- and Δ^9-*trans*-THC Family



Diels–Alder approach for the rapid construction of a series of *trans*-6a,7,10,10a-tetrahydro-6*H*-benzo[*c*]chromenes and for the synthesis of Δ^8-*trans*-THC (**4**) in both enantiomeric pure forms.[1e]

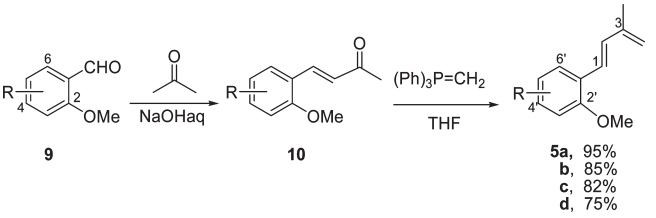
Among the natural cannabinoids isolated from the Indian hemp, the most prominent is (−)-Δ^9-THC, which has a 6a,7,8,10a-tetrahydro-6*H*-benzo[*c*]chromene core structure. Despite the increased need for new broadly substituted Δ^9-*cis*-THCs and Δ^9-*trans*-THCs, their synthesis remains a highly labor-intensive process.[7] We envisioned as a new eco-friendly method for accessing substituted *cis*- and *trans*-Δ^9-THCs family a strategy illustrated in Scheme 1. The diastereoselective Diels–Alder reaction of 3-methyl-1-(alkoxy/alkyl-substituted phenyl)buta-1,3-dienes **5** with methyl vinyl ketone (**6x**) and methyl acrylate (**6y**) is the cornerstone of our strategy, because it allows the expedient generation of the carbon skeleton and secures the proper stereochemistry at the cyclohexene ring stereocenters. The 6a,7,8,10a-tetrahydro-6*H*-benzo[*c*]chromene system can then be obtained by Grignard addition, demethylation, and cyclyzation (Scheme 1).

In the present study we report (i) investigation of the Diels–Alder reaction of 3-methyl-1-(alkoxy/alkyl-substituted phenyl)buta-1,3-dienes **5** with methyl vinyl ketone (**6x**) and methyl acrylate (**6y**) in green solvents[10] as reaction medium and under high pressure; (ii) the conversion of selected cycloadducts into their corresponding Δ^9-*cis*- and Δ^9-*trans*-THCs; and (iii) a route for obtaining Δ^9-*trans*-THC in both enantiomeric pure forms based on the SAMP-hydrazone method.[1e]

RESULTS AND DISCUSSION

3-Methyl-1-(alkoxy/alkyl-substituted phenyl)buta-1,3-dienes Synthesis. The necessary 1,3-butadienes **5** can be readily synthesized in high yields (75–95%) and with total selectivity by the Wittig reaction[11] of the corresponding (*E*)-benzylideneacetones **10**[1e] (Scheme 2).

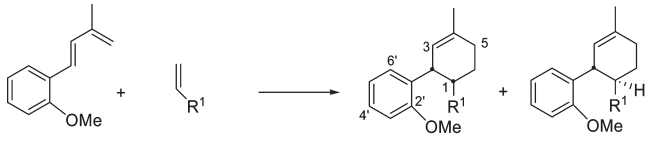
Scheme 2. Synthesis of 3-Methyl-1-(alkoxy/alkyl-substituted phenyl)buta-1,3-dienes



Diels–Alder Reactions of 3-Methyl-1-(alkoxy/alkyl-substituted phenyl)buta-1,3-dienes 5 with Methyl Vinyl Ketone (6x) and Methyl Acrylate (6y) under Atmospheric and High-Pressure Conditions. The Diels–Alder reaction between **5** and **6** is the key step of our strategy as this allows access to the 6a,7,8,10a-tetrahydro-6*H*-benzo[*c*]chromene skeleton. The control of *endo*/*exo* diastereoselectivity of the cycloaddition reactions is of particular importance, as it secures the correct *cis*/*trans* stereochemistry at the C1 and C2 stereocenters of the cycloadducts, which selectively allows access to the Δ^9-*cis*- and *trans*-Δ^9-THCs (see Scheme 1). There are relatively few examples of Diels–Alder reaction of 1-aryl-1,3-butadienes in the literature, and examples of cycloaddition reactions of **5** with dienophiles of type **6** are particularly rare. Thus, it became clear that optimizing the Diels–Alder reaction of **5** with dienophiles of type **6** would not be a trivial task. For example, it has been reported that 1-aryl-1,3-butadienes and 1-aryl-2,3-dimethyl-1,3-butadienes react with methyl acrylate under thermal conditions (80–100 °C) with low to moderate *endo*/*exo* distereoselectivities, to give mixtures of the

dx.doi.org/10.1021/jo200796b |*J. Org. Chem.* 2011, 76, 5392–5403

Table 1. Diels–Alder Reactions of (*E*)-3-Methyl-1-(2′-methoxyphenyl)buta-1,3-diene (5a) with Methyl Vinyl Ketone (6x) and Methyl Acrylate (6y) under Atmospheric and High-Pressure Conditions



5a **6x**, R^1 = COMe; **y**, R^1 = CO_2Me **7ax**, R^1 = COMe; **ay**, R^1 = CO_2Me **8ax**, R^1 = COMe; **ay**, R^1 = CO_2Me

entry	dienophile[a]	medium[b]	*t* (h)	*P* (kbar)	*T* (°C)	products[d]	yield[e] (%)
1	**6x**	PhMe	18	10^{-3}	reflux	**7ax**/**8ax** (3:1)	47
2	**6x**	EtOH	21	10^{-3}	reflux	**7ax**/**8ax** (4:1)	48
3	**6x**	EtOH	76	10^{-3}	22	**7ax**/**8ax** (4:1)	75, 60[f]
4	**6x**	H_2O	44	10^{-3}	50	**7ax**/**8ax** (3:1)	80, 58[f]
5	**6x**	CH_2Cl_2	3	10^{-3}[c]	22	**7ax**/**8ax** (4:1)	55
6	**6x**	EtOH	16	9	22	**7ax**/**8ax** (9:1)	92, 80[f]
7	**6x**	CH_2Cl_2	14	9	22	**7ax**/**8ax** (5:1)	73, 58[f]
8	**6x**	$CF_3(CF_2)_4CF_3$	6	9	22	**7ax**/**8ax** (4:1)	41
9	**6x**	H_2O	14	9	22	**7ax**/**8ax** (4:1)	23
10	**6x**	H_2O/EtOH (1:1)	14	9	22	**7ax**/**8ax** (5.7:1)	25
11	**6x**	H_2O/EtOH (3:1)	14	9	22	**7ax**/**8ax** (7.3:1)	30
12	**6y**	EtOH	23	10^{-3}	80	**7ay**/**8ay** (4:1)	55
13	**6y**	H_2O	50	10^{-3}	50	**7ay**/**8ay** (4:1)	45
14	**6y**	CH_2Cl_2	14	9	22	**7ay**/**8ay** (5.7:1)	46
15	**6y**	EtOH	16	9	22	**7ay**/**8ay** (9:1)	92, 81[f]

[a] Two equivalents of dienophile were used. [b] Diene concentration = 0.1 M. [c] 10 mol % of $HfCl_4 \cdot THF$ was used. [d] *cis*:*trans* diastereoisomeric ratio was determined by GC and ^1H NMR analyses. [e] Combined isolated yields of distereoisomers **7** and **8**. [f] Yield of purified cycloadduct **7**.

cis/*trans* adducts in ratios of 1.3/1 to 2.5/1 in moderate yields (50–60%).[12] However, to the best of our knowledge, no examples of Diels–Alder reactions between 3-methyl-1-(alkoxy/alkyl-substituted phenyl)-1,3-butadienes **5** and dienophiles **6** have been reported, except the cycloaddition reaction between diene **5d** and methyl vinyl ketone **6x**, which was reported to occur at high temperature (130 °C) and to give unspecified mixtures of the *cis*/*trans* cycloadducts in ratios of 2:1 and 1:6 at 130 and 200 °C, respectively.[8a]

Thus, the Diels–Alder reactions of 3-methyl-1-(2′-methoxyphenyl)buta-1,3-diene **5a** with dienophiles **6x,y** were chosen as representative and investigated under various atmospheric and high-pressure conditions in green solvents (ethanol or water) as the reaction medium, to find efficient (high yield and selectivity) and eco-friendly conditions for these transformations. The results of the optimization study are summarized in Table 1.

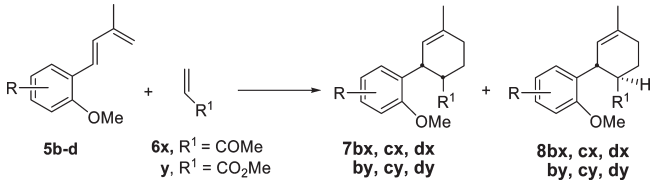
Under atmospheric or high-pressure conditions, the cycloadditions of **5a** with **6x,y** were always totally regioselective. Hovewer, this regiochemical behavior is typical of 1-substituted 1,3-butadienes and can be explained on the basis of frontier molecular orbital teory[9h]

Under atmospheric pressure (10^{-3} kbar), heating at reflux temperature 3-methyl-1-(2′-methoxyphenyl)buta-1,3-diene **5a** with methyl vinyl ketone **6x** in toluene or ethanol solution led to 3:1 and 4:1 mixtures of the *endo*-cycloadduct **7ax** and *exo*-cycloadduct **8ax**, respectively, in low isolated yields (47% and 48%, respectively) (Table 1, entries 1 and 2). Cycloaddition reactions at ambient pressure in ethanol or water gave good yields (75% and 80%, respectively) when the reaction temperatures were lowered to 22 and 50 °C, respectively, although the prevalences of *endo*-adduct **7ax** (*endo*/*exo* 4:1 and 3:1, respectively) was still not satisfactory (Table 1, entries 3 and 4). Similarly, methyl acrylate (**6y**) reacted with **5a** at normal pressure in ethanol or water as the reaction medium to provide a 4:1 mixture of the *endo*/*exo*-cycloadducts **7ay** and **8ay** in moderate yields (55% and 45%, respectively) (Table 1, entries 12 and 13). Considering that enhanced *endo*-diastereoselectivity and higher yields of the Diels–Alder reactions are generally achieved using Lewis acid catalysis and/or high pressure,[9] we studied the cycloaddition of **5a** with **6x** under Lewis acid catalysis and high-pressure conditions. However, the reaction of **5a** with **6x** in the presence of $HfCl_4 \cdot 2THF$ at ambient pressure and temperature led again to a 4:1 mixture of *endo*/*exo*-cycloadducts **7ax** and **8ax** in moderate yield (55%), although with a reduced reaction time (Table 1, entry 5). Instead, when using hyperbaric conditions (9 kbar pressure) and ethanol as the reaction medium, remarkably superior *endo*-diastereoselectivity (**7ax**/**8ax**, 9:1) and good yield (92%) were finally obtained in a reduced reaction time (16 h) and at room temperature (Table 1, entry 6).

To further improve both the yield and the *endo*-diastereoselectivity, we investigated the solvent effect at 9 kbar pressure. Changing the solvent from methylene chloride, known to be the best solvent in high-pressure experiments mainly because of its low freezing point, to water, ethanol/water mixtures, and perfluorohexane, known to have solvophobic effects,[13] did not improve either the yield or the *endo*-distereoselectivity of this Diels–Alder reaction (Table 1, entries 7–11). In the case of the cycloaddition of **5a** with methyl acrylate (**6y**), analogous to the above reports for **6x**, hyperbaric conditions (9 kbar) and use of ethanol as the reaction medium provided the best yield (92%) and *endo*-diastereoselectivity (**7ay**/**8ay**, 9:1).

dx.doi.org/10.1021/jo200796b |*J. Org. Chem.* 2011, 76, 5392–5403

Table 2. Diels–Alder Reactions of 3-Methyl-1-(alkoxy/alkyl-substituted phenyl)buta-1,3-dienes (5b–d) with But-3-en-2-one (6x) and Methyl Acrylate (6y) under Atmospheric and High-Pressure Conditions



entry	diene[a]	dienophile[b]	medium	t (h)	P (kbar)	T (°C)	products[c]	yield[d] (%)
1	**5b**	**6x**	EtOH	20	10^{-3}	80	**7bx**/**8bx** (2.5:1)	60
2	**5b**	**6x**	H_2O	21	10^{-3}	50	**7bx**/**8bx** (4:1)	57
3	**5b**	**6x**	EtOH	24	9	21	**7bx**/**8bx** (6:1)	88, 74[e]
4	**5b**	**6y**	EtOH	28	10^{-3}	80	**7by**/**8by** (2.7:1)	45
5	**5b**	**6y**	H_2O	37	10^{-3}	50	**7by**/**8by** (3:1)	55
6	**5b**	**6y**	EtOH	24	9	21	**7by**/**8by** (5.3:1)	85, 68[e]
7	**5c**	**6x**	EtOH	16	10^{-3}	80	**7cx**/**8cx** (2.7:1)	72, 48[e]
8	**5c**	**6x**	H_2O	46	10^{-3}	50	**7cx**/**8cx** (2.6:1)	62
9	**5c**	**6x**	EtOH	18	9	21	**7cx**/**8cx** (5.5:1)	90, 70[e]
10	**5c**	**6y**	EtOH	20	10^{-3}	80	**7cy**/**8cy** (3:1)	43
11	**5c**	**6y**	H_2O	120	10^{-3}	50	**7cy**/**8cy** (2.5:1)	65
12	**5c**	**6y**	EtOH	18	9	21	**7cy**/**8cy** (5:1)	80, 65[e]
13	**5d**	**6x**	EtOH	24	10^{-3}	80	**7dx**/**8dx** (3.3:1)	69
14	**5d**	**6x**	H_2O	46	10^{-3}	50	**7dx**/**8dx** (2.8:1)	45
15	**5d**	**6x**	H_2O	22	10^{-3}	80	**7dx**/**8dx** (2.7:1)	67
16	**5d**	**6x**	EtOH	36	9	21	**7dx**/**8dx** (6:1)	92, 72[e]
17	**5d**	**6y**	EtOH	24	10^{-3}	80	**7dy**/**8dy** (2.8:1)	48
18	**5d**	**6y**	H_2O	120	10^{-3}	50	**7dy**/**8dy** (2.4:1)	67
19	**5d**	**6y**	EtOH	36	9	21	**7dy**/**8dy** (4.7:1)	83, 65[e]

[a] Diene concentration, 0.1 M. [b] Two equivalents of dienophile were used. [c] The *cis-trans* diastereoisomeric ratio was determined by GC and ^{1}H NMR analyses. [d] Combined isolated yields of distereoisomers **7** and **8**. [e] Yield of purified cycloadduct **7**

The study was then extended to the Diels–Alder reactions of other 3-methyl-1-(alkoxy/alyl-substituted phenyl)buta-1,3-dienes **5b–d** with dienophiles **6x,y** to determine the flexibility of this approach for the selective construction of the Δ^9-*cis*- and Δ^9-*trans*-THC skeleton. The alkoxy group in the 2′-position of arylbutadienes **5** is essential for pyran ring formation of the THCs family (see Scheme 1), whereas those in the 4′-position and 6′-position are useful for access to various desoxy-cannabinoids derivatives and to the characteristic 1-hydroxy group of natural cannabinoids, respectively (Figure 1). Results of the optimized thermal and high-pressure reaction conditions are reported in Table 2.

As with **5a**, the cycloadditions of **5b–d** with both dienophiles **6x,y** carried out under normal or high-pressure conditions were always totally regioselective. (Table 2).

Under atmospheric conditions, the Diels–Alder reactions of **5b–d** with **6x** in ethanol and water at 80 and 50 °C respectively, led to the isolation of the expected distereomeric cycloadducts in moderate yields (45–72%) as mixtures of the *endo*/*exo* diastereoisomers **7bx–dx** and **8bx–dx** in ratios of 2.5:1 to 4:1 (Table 2, entries 1, 2, 7, 8, 13, and 14). The thermal reactions of **5d** with **6x** in ethanolic medium were also studied using 3 or 5 equiv of **6x** and at various reaction temperatures (22, 50, and 65 °C), although neither an increase in yield nor of *endo*-diastereoselectivity were ever observed. Unexpectedly, the higher electron-donating character of the phenyl moiety of dienes **5b–d** when compared to **5a** did not translate into higher isolated yields, presumably because of steric hindrance.

With methyl acrylate (**6y**), the thermal cycloadditions of **5b–d** occurred in aqueous medium with comparable yields (55–67%) although over longer reaction times (37–120 h), with respect to **6x** (Table 2, entries 5, 11 and 18), whereas in ethanol as reaction medium, the same cycloadditions generally gave lower yields (43–48%) (Table 2, entries 4, 10 and 17).

Comparison across the data reported in Table 2 indicates that once again high pressure was the most efficient and eco-friendly method of activation,[9g] as this allowed the reactions to proceed with better yields and selectivities under much milder reaction conditions in a green reaction medium and without the use of any metallic catalyst. Thus, under 9 kbar pressure (in the highest yielding cases), dienes **5b–d** reacted in a highly *endo*-stereoselective fashion with **6x** in ethanolic solution at room temperature to give in high yield (88–92%) mixtures of the corresponding *endo*/*exo* cycloadducts **7bx**/**8bx**, **7cx**/**8cx** and **7dx**/**8dx** (Figure 2), in the ratios 6:1, 5.5:1 and 6:1, respectively (Table 2, entries 3, 9, and 16). Separation by chromatography on silica gel led the pure *endo*-cycloadducts **7bx**, **7cx**, and **7dx** in 74%, 70% , and 72% yields, respectively. With methyl acrylate (**6y**), under identical conditions, the cycloadditions of **5b–d** again gave good isolated yields of the diastereomeric cycloadducts (80–88%), although they were slightly less *endo*-diastereoselective, producing mixtures of *endo*/*exo* cycloadducts **7by**/**8by**, **7cy**/**8cy**, and

dx.doi.org/10.1021/jo200796b |*J. Org. Chem.* 2011, 76, 5392–5403

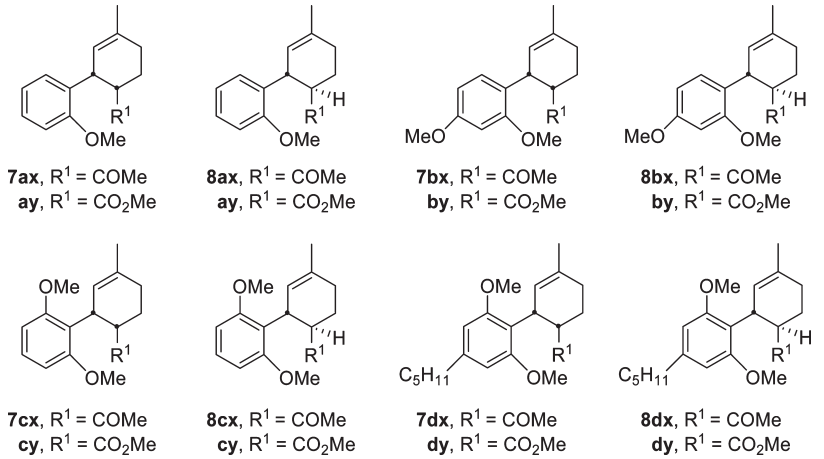
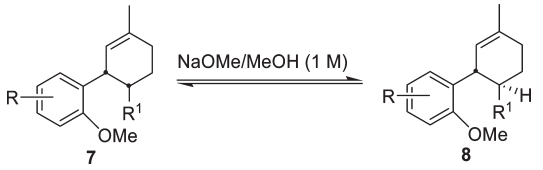


Figure 2. Diels–Alder cycloadducts.

Table 3. Equilibrium Constants for the *cis-trans* Isomerism of Cycloadducts 7 and 8



cycloadduct pairs[a]	*t* (h)	*T* (°C)	yield (%)	*K*[b]
7ax-8ax	24	22	79	99
7ay-8ay	20	50	85	19
7bx-8bx	24	22	78	19
7by-8by	96	50	75	9
7cx-8cx	27	22	73	19
7cy-8cy	72	50	76	6
7dx-8dx	22	22	95	33
7dy-8dy[7m]	72	65	91	33

[a] Concentration of cycloadducts **7**, 0.18 M. [b] *K*, *trans*-cycloadduct **8**/*cis*-cycloadduct **7** ratio. Based on GC analysis.

7dy/**8dy** (Figure 2) in the ratios of 5.3:1, 5:1, and 4.7:1, respectively (Table 2, entries 6, 12, and 19). However, the good *endo*-diastereoselectivity allowed the isolation in pure forms of the cycloadducts **7by**, **7cy**, and **7dy** in 65–68% yields, by column chromatography on silica gel.

Application to the Synthesis of the Δ⁹-*cis*- and Δ⁹-*trans*-THCs. With a large number of the *cis*-methoxy-substituted cyclohexenyl-benzenes **7** on hand, it appeared useful to investigate their stabilities with respect to the *cis-trans* isomerization, to acquire a body of thermodynamic data of possible use to also access the Δ⁹-*trans*-THCs family.

Equilibria of the *endo*/*exo* cycloadducts **7**/**8** epimers were established in methanolic sodium methoxide, and the optimal results are given in Table 3. Inspection of the equilibrium data reveals that the *trans*-epimers **8** with an pseudo equatorial C(2)-aryl group are more stable than the *cis*-isomers **7** with a pseudo axial C(2)-aryl group (Figure 3).

We then turned our attention to the synthesis of Δ⁹-*cis*-THC (**1**) and Δ⁹-*trans*-THC (**2**). Thus, starting from pure *endo*-cycloadduct **7dx**, methylation with CH_3MgBr in toluene at 60 °C resulted in the formation of the corresponding tertiary alcohol **11** (95% yield), which was subjected to monodemethylation with NaSMe in DMF,[1e,14] to give diol **12** in an 85% yield (Scheme 3). Our efforts were next directed toward forming the pyran ring for the construction of Δ⁹-*cis*-THC (**1**). However, all of our attempts to achieve cyclyzation of **12** under the standard conditions ($ZnBr_2$, $MgSO_4$)[1e,7j,7m,8c] used previously for the *trans*-THCs were unsuccessful. Formation of the desired, cyclyzed ether **13** was achieved in a 65% isolated yield by heating **12** in benzene at 75 °C for 0.5 h in the presence of a catalytic amount of TsOH.[15] Next, according to the literature data,[1e,7m] the remaining methoxy group on **13** was removed with NaSMe (10 equiv) in DMF at 140 °C, to provide Δ⁹-*cis*-THC[7a,d,g] (**1**) in 70% yield (Scheme 3). The Δ⁹-*cis*-THC (**1**) hed been formed previously in low yields as a byproduct in some syntheses of the *trans*-isomer **2**.[7a,d,g]

The synthesis of Δ⁹-*trans*-THC (**2**) from ester **8dy** has been reported in literature[7m] (Scheme 3). Alternatively, we synthesized Δ⁹-*trans*-THC (**2**) from pure ketone **8dx** through methylation and subsequent monodeprotection to known diol **14**,[7j,m,8d] which was then converted into **2** by pyran ring formation and demethylation, according to the literature data[7j,m] (Scheme 3).

Synthesis of (*R,R*)-(−)- and (*S,S*)-(+)-Δ⁹-THCs (2). With the rapid and efficient entry into racemic Δ⁹-*trans*-THC (**2**) via this high-pressure Diels–Alder approach, we wanted to explore the feasibility of obtaining enantiomerically enriched **2** using SAMP (**15**) as the reagent for resolution of the cycloadduct **8dx**, which we previously used successfully for resolution of Δ⁸-*trans*-THC (**4**).[1e] Thus, when the acetyl derivative **8dx** was treated with commercially available SAMP (**15**) a mixture of the two diastereoisomeric SAMP-hydrazones **16** were obtained. The mixture was chromatographed over silica gel, eluting with 95:5 petroleum ether/Et_2O to give diastereomerically pure (*S,R,R*)-(+)-**16** $[\alpha]_D$ = +54 (*c* 1.57, $CHCl_3$) and (*S,S,S*)-(+)-**16** $[\alpha]_D$ = +156 (*c* 1.25, $CHCl_3$) in 37% and 40% yields, respectively. Upon hydrolysis of the corresponding SAMP-hydrazones **16** with oxalic acid,[1e] enantiomerically pure (*R,R*)-(−)-**8dx** $[\alpha]_D$ = −98 (*c* 2.28, $CHCl_3$) and (*S,S*)-(+)-**8dx** $[\alpha]_D$ = +101 (*c* 1.68, $CHCl_3$) were obtained in 75% and 65% yield, respectively. It should be noted that the SAMP (**15**) was recovered in a 64% yield. Confirmation that no racemization had occurred under the reaction conditions was achieved by reamination of (*R,R*)-(−)-**8dx** with (*S*)-(−)-SAMP **15** to provide (*S,R,R*)-(+)-**16** as a single diastereomer (75%).

dx.doi.org/10.1021/jo200796b |*J. Org. Chem.* 2011, 76, 5392–5403

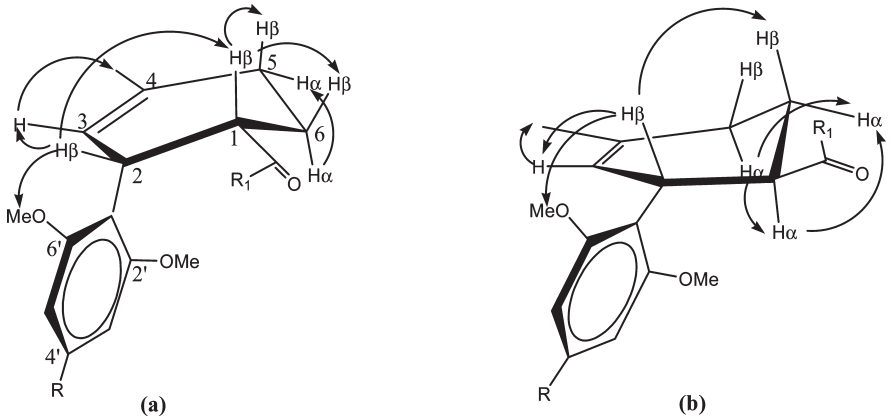
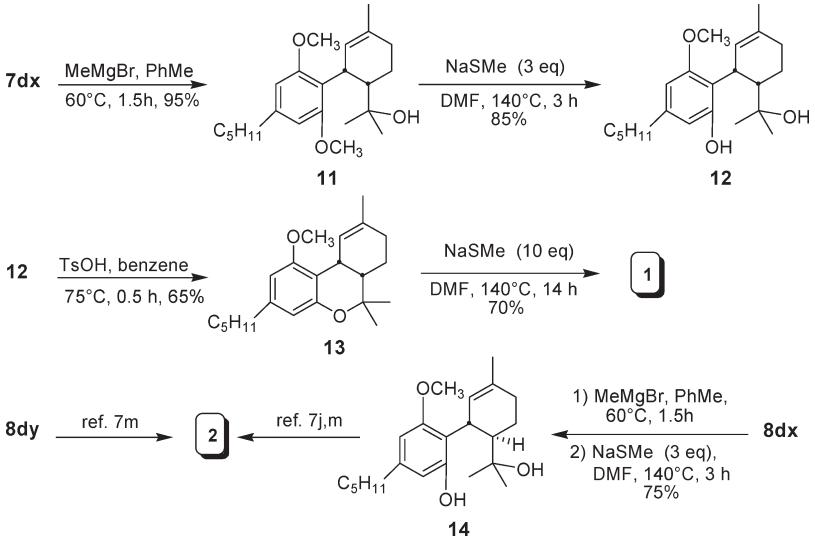


Figure 3. Structures assigned to (a) cycloadducts **7cx** (R = H, $R_1 = CH_3$) and **7dx** (R = C_5H_{11}, $R_1 = CH_3$) and (b) cycloadducts **8cx** (R = H, $R_1 = CH_3$) and **8dx** (R = C_5H_{11}, $R_1 = CH_3$). Arrows indicate the observed 2D-NOESY correlations.

Scheme 3. Racemic Synthesis of Δ^9-*cis*-THC 1 and Δ^9-*trans*-THC 2

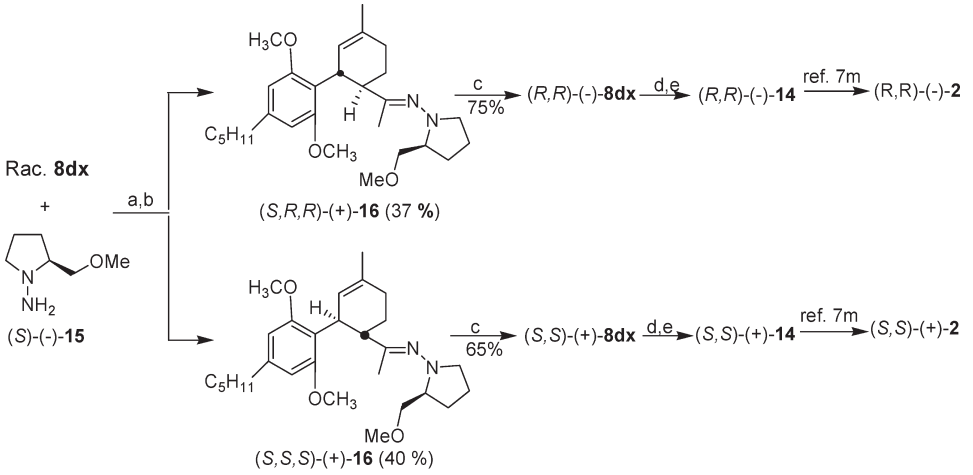


With the same sequence established for the synthesis of racemic Δ^9-*trans*-THC (**2**), the (*R*,*R*)-(−)-**2** $[\alpha]_D$ = −148 (*c* 0.35, $CHCl_3$) (lit.[7m] $[\alpha]_D$ = −152 (*c* 0.46, $CHCl_3$)) and (*S*,*S*)-(+)-Δ^9-THC **2** $[\alpha]_D$ = +143 (*c* 0.39, $CHCl_3$) (lit.[8c] $[\alpha]_D$ = +141 (*c* 0.55, $CHCl_3$)) were prepared from (*R*,*R*)-(−)-**8dx** and (*S*,*S*)-(+)-**8dx**, respectively, through the key intermediate diols (*R*,*R*)-(−)-**14** $[\alpha]_D$ = −48 (*c* 1.45, $CHCl_3$) (lit.[7m] $[\alpha]_D$ = −52 (*c* 0.79, $CHCl_3$)) and (*S*,*S*)-(+)-**14** ($[\alpha]_D$ = +46 (*c* 0.92, $CHCl_3$)) (Scheme 4).

Structural Analysis. The structures of all of the compounds were inferred from the analysis of their ^{1}H NMR and ^{13}C NMR spectra. The pertinent data are given in the Experimental Section. The (*E*)-configuration of the carbon−carbon double bond for all of the 1-aryl-1,3-butadienes **5** was confirmed from the 16.4−16.6 Hz coupling constant values measured for $^3J_{1,2}$. The regiochemistry of the methyl group and the *cis*/*trans* stereochemical assignment of all cycloadducts were based mainly on 2D-COSY, NOESY, and HMQC experiments performed on **7cx**, **7dx**, **8cx**, and **8dx** (Figure 3). Inspection of the ^{1}H−^{1}H and ^{1}H−^{13}C connectivities of compounds **7cx**, **7dx**, **8cx**, and **8dx**, together with their NOESY correlation peaks between H-2, H-3, and 4-Me protons for these compounds, revealed the regiochemistry of the methyl group at C-4. Furthermore, the presence of a NOESY correlation peak was observed between H-1, H-2, and H-6β and between H-2, H-3, and the 6′-OMe protons for cycloadducts **7cx** and **7dx** (Figure 3a), thus revealing the *cis*-relationship of H-1 and H-2 for **7cx** and **7dx** (Figure 3a). However, the *trans*-relationship of H-1 and H-2 for adducts **8cx** and **8dx** followed from the NOESY correlation peaks observed between H-2, H-3, and H-6β and between H-1, H-5α, and H-6α, together with the absence of a correlation peak between H-1 and H-2 (Figure 3b). Support for the structure depicted in Figure 3a for all of the *cis*-adducts **7** was given by the large similarities in the proton and carbon shifts of the comparable sites of these adducts with **7cx** and **7dx**. Similarly, the structure for all of the *trans*-adducts **8** (Figure 3b) was given from the similarity of the proton and carbon shifts of comparable sites of these adducts with **8cx** and **8dx**. Finally, confirmation of the structures assigned to adducts **7** and **8** followed also from the conversion of **7dx** and **8dx** into the known Δ^9-*cis*-THC (**1**) and Δ^9-*trans*-THC (**2**), respectively.

dx.doi.org/10.1021/jo200796b |*J. Org. Chem.* 2011, 76, 5392–5403

Scheme 4. Resolution of Racemic 8dx via SAMP-Derivatization and Synthesis of (*R,R*)-(−)- and (*S,S*)-(+)-Δ^9-THCs 2



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 NaSMe, DMF, 140°C, 3 h .

CONCLUSIONS

A novel high-yielding route to the Δ^9-*cis*- and Δ^9-*trans*THC families via Diels−Alder reactions of substituted 1-aryl-3-methyl-1,3-butadienes **5** with methyl vinyl ketone (**6x**) and methyl acrylate (**6y**) was developed. Hyperbaric activation of the cycloaddition reactions allowed the corresponding cycloadducts to be prepared in excellent yields and with high *endo*-diastereoselectivity, under mild reaction conditions and without any metal catalyst. Along with the use of a green ethanolic medium, this makes this approach to the 6a,7,8,10a-tetrahydro-6*H*-benzo[*c*]chromene motif (i.e., Δ^9-*cis*- and Δ^9-*trans*-THC) chemically efficient and environmentally compatible. The power of this approach lies in the ability of the high pressure to activate efficiently and *endo*-diastereoselectively the Diels−Alder reactions allowing access to *cis*-cyclohexenyl-benzene cycloadducts **7** and their *trans*-epimers **8** by base-catalyzed equilibration. These are useful precursors for the synthesis of broadly substituted *cis*- and *trans*-6a,7,8,10a-tetrahydro-6*H*-benzo[*c*]chromenes-based privileged structures (i.e., the Δ^9-THC family) for use in bioassays and SAR studies. Application to the synthesis of Δ^9-*cis*-THC **1** was accomplished from selected Diels−Alder *endo*-cycloadduct **7dx** by Grignard addition, demethylation, and pyran ring formation, while access to Δ^9-*trans*-THC **2** has been achieved with the same sequence, through the prior conversion of the *endo*-adduct **7dx** into the epimer *exo*-adduct **8dx** in methanolic sodium methoxide. Finally, easy and efficient resolution of cycloadduct **8dx** by the SAMP-hydrazone method provided the rapid synthesis of Δ^9-*trans*-THC **2** in both enantiomeric pure forms.

EXPERIMENTAL SECTION

General Methods. NMR spectra were recorded at 400 or 200 MHz for proton and 100.6 or 50.3 MHz for carbon nuclei. GC−MS analyses were carried out by using a 70 eV electron energy EI. GC analyses were performed with an SPB-5 fused silica capillary column (30 m, 0.25 mm diameter) on an "on column" injector system and FID detector with hydrogen as the carrier gas. IR spectra were recorded with a FT-IR instrument, using $CHCl_3$ as solvent. Melting points are uncorrected. Hyperbaric experiments were conducted on a Unipress LV30/16 apparatus. The aryl buta-1,3-dienes **5a**,[16] **5c**,[16c] and **5d**[8a,16c] are known in the literature. The synthesis of aryl buta-1,3-dienes **5a**−**d** was carried out according a previous procedre[11] by Wittig reaction of the corresponding (*E*)-benzylideneacetones **10** (Scheme 2). Benzylideneacetones **10** were prepared by aldol condensation of benzaldehydes **9** and acetone, as previously reported by us.[1e] Dienophiles **2** were purchased and used without further purification. The products were purified by column chromatography carried out on silica gel (230−400 mesh), using petroleum ether/ethyl acetate or petroleum ether/diethyl ether mixtures as eluent

The complete NMR structure assignments for all the new compounds were based on the relevant $J_{H,H}$ coupling constant values and on COSY, NOESY, and HETCOR experiments.

2′,4′-Dimethoxy-1-((*E*)-3-methylbuta-1,3-dienyl)benzene (5b). Oil; IR ($CHCl_3$) 3026, 3013, 2945, 2843, 1606, 1505 cm^{-1}; ^1H NMR (400 MHz; C_6D_6) δ 2.03 (s, 3H, CH_3), 3.36 (s, 3H, OCH_3), 3.45 (s, 3H, OCH_3), 5.09 (s, 1H, H-4), 5.21 (s, 1H, H-4), 6.47 (s, 1H, H-3′), 6.48 (d, 1H, J = 8.7 Hz, H-5′), 7.08 (d, 1H, J = 16.3 Hz, H-1), 7.29 (d, 1H, J = 16.3 Hz, H-2), 7.53 (d, 1H, J = 8.7 Hz, H-6′); ^{13}C NMR (400 MHz; $CDCl_3$) δ 18.7, 55.3, 55.4, 98.4, 104.9, 115.7, 119.5, 123.0, 127.0, 130.1, 142.8, 157.8, 160.3; MS *m*/*e* (rel intensity) 77 (21), 101 (21), 115 (36), 128 (29), 129 (26), 158 (81), 159 (27), 172 (23), 173 (53), 174 (54), 18 (45), 189 (100), 190 (27), 204 (M^+, 100). Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.34; H, 7.84.

2′,6′-Dimethoxy-1-((*E*)-3-methylbuta-1,3-dienyl)benzene (5c)[16c]. White solid, mp 38−39 °C (*n*-hexane); IR ($CHCl_3$) 3013, 2954, 2840, 1584, 1473 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 1.89 (s, 3H, CH_3), 3.73 (s, 6H, OCH_3, OCH_3), 4.92 (s, 1H, H-4), 4.97 (s, 1H, H-4), 6.44 (d, 2H, J = 8.3 Hz, H-3′, H-5′), 6.76 (d, 1H, J = 16.5 Hz, H-1), 7.01 (t, 1H, J = 8.3 Hz, H-4′), 7.22 (d, 1H, J = 16.5 Hz, H-2); ^{13}C NMR (400 MHz; $CDCl_3$) δ 18.3, 55.6 (2C), 103.9 (2C), 114.7, 116.2, 119.7, 127.8, 135.4, 143.6, 158.4 (2C); MS *m*/*e* (rel intensity) 77 (11), 91 (19), 115 (21), 128 (16), 129 (13), 141 (15), 158 (100), 159 (20), 173 (100), 174 (30), 189 (28), 204 (M^+, 100). Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.56; H, 7.83.

2′,6-Dimethoxy-1-((*E*)-3-methylbuta-1,3-dienyl)-4′-pentylbenzene (5d)[8a,16c]. Oil; IR ($CHCl_3$) 2988, 2935, 2859, 1569, 1458 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 0.95 (t, 3H, J = 6.8 Hz, CH_3), 1.29−1.42 (m, 4H, CH_2CH_2), 1.62−1.70 (m, 2H, CH_2), 2.04 (s, 3H, CH_3), 2.60 (t, 2H, J = 7.8 Hz, CH_2), 3.85 (s, 6H, OCH_3), 5.04 (s,

dx.doi.org/10.1021/jo200796b |*J. Org. Chem.* 2011, 76, 5392–5403

1H, H-4), 5.10 (s, 1H, H-4), 6.41 (s, 2H, H-3′, H-5′), 6.91 (d, 1H, J = 16.5 Hz, H-1), 7.36 (d, 1H, J = 16.5 Hz, H-2); ^{13}C NMR (400 MHz; $CDCl_3$) δ 13.9, 18.2, 22.3, 30.1, 30.9, 36.5, 55.4 (2C), 104.0 (2C), 111.5, 115.1, 119.9, 128.1, 134.0, 143.5, 143.6, 158.3; MS m/e (rel intensity) 43 (13), 158 (26), 171 (11), 172 (11), 173 (66), 174 (12), 243 (49), 259 (12), 274 (M^+, 100). Anal. Calcd for $C_{18}H_{26}O_2$: C, 78.79; H, 9.55. Found: C, 78.71; H, 9.48.

General Procedure for the Diels−Alder Reaction of 1-Arylbuta-1,3-dienes (5a−d) with Methyl Vinyl Ketone (6x) and Methyl Acrylate (6y). The cycloaddition reactions of 1-arylbutadienes **5** with dienophiles **6** were accomplished (A) at normal pressure-(10^{-3} kbar) and (B) under 9 kbar pressure conditions. The details are given in Tables 1 and 2.

Condition (A). Dienophile **6** (3 mmol) and a few crystals of hydroquinone were added to a solution of arylbutadiene **5** (1.5 mmol) in 15 mL of the solvent and the resulting mixture was poured into an oil bath under magnetic stirring at the indicated reaction temperature and for the indicated reaction time. The cooled mixture was then poured into saturated brine (15 mL) and extracted twice with diethyl ether. The dried extract (Na_2SO_4) was evaporated under vacuum and chromatographed over silica gel. Elution with 10% to 25% mixtures of diethyl ether/petroleum ether gave the pure cycloadducts **7**.

Condition (B). A solution of arylbutadiene **5** (1.5 mmol) in 10 mL of solvent was placed in a 15 mL Teflon vial. Dienophile **6** (3 mmol) and a few crystals of hydroquinone were then added, and the vial was filled with the solvent. The vial was closed and kept at 9 kbar at the indicated temperature for the appropriate time. After depressurizing, the mixture was worked up and purified as above, giving the pure cycloadducts **7**.

***rel*-1-((1*S*,2*R*)-2-(2′-Methoxyphenyl)-4-methylcyclohex-3-enyl)ethanone (7ax).** White solid, mp 72−73 °C (*n*-hexane); IR ($CHCl_3$) 1705 (C═O) cm^{-1}; ^{1}H NMR (400 MHz; $CDCl_3$) δ 1.42 (ddd, 1H, J = 13.6, 6.4, 2.7 Hz, H-6β), 1.63 (s, 3H, CH_3), 1.66 (m, 1H, J = 13.4, 11.9 Hz, H-6α), 1.85−1.92 (m, 1H, H-5β), 1.97 (dd, 1H, J = 17.5, 6.4 Hz, H-5α), 1.88 (s, 3H, CH_3C═O), 2.82 (ddd, 1H, J = 11.9, 5.4, 2.7 Hz, H-1), 3.58 (s, 3H, OCH_3), 4.16 (s broad,1H, H-2), 5.26 (d broad, 1H, H-3), 6.62 (d, 1H, J = 8.0 Hz, H-3′), 6.74 (t, 1H, J = 7.5 Hz, H-5′), 7.01 (m, 2H, H-4′, H-6′); ^{13}C NMR (400 MHz; $CDCl_3$) δ 14.0, 19.8, 23.4, 29.5, 29.7, 34.8, 51.3, 54.5, 109.6, 119.9, 122.8, 127.7, 128.6, 130.7, 134.9,156.7, 210.7; MS m/e (rel intensity) 43 (57), 77 (26), 91 (36), 95 (34), 107 (100), 115 (22), 137 (78), 145 (37), 147 (67), 201 (46), 211 (99), 226 (35), 244 (M^+, 70). Anal. Calcd for $C_{16}H_{20}O_2$: C, 78.65; H, 8.25. Found: C, 78.56; H, 8.23.

***rel*-(1*S*,2*R*)-Methyl 2-(2′-Methoxyphenyl)-4-methylcyclohex-3-enecarboxylate (7ay).** White solid, mp 51−52 °C (*n*-hexane); IR ($CHCl_3$) 1731 (C═O) cm^{-1}; ^{1}H NMR (400 MHz; $CDCl_3$) δ 1.57 (ddd, 1H, J = 15.1, 6.5, 3.1 Hz, H-6β), 1.62 (s, 3H, CH_3), 1.75 (ddd, 1H, J = 13.5, 11.0, 6.0 Hz, H-6α), 1.90 (m, 1H, J = 16.7, 8.4 Hz, H-5β), 2.01 (dt broad, 1H, J = 17.0 Hz H-5α), 2.78 (m, 1H, J = 11.0, 5.8, 3.1 Hz, H-1), 3.26 (s, 3H, CH_3OC═O), 3.63 (s, 3H, OCH_3), 4.10 (s, 1H, H-2), 5.23 (s broad, 1H, H-3), 6.64 (d, 1H, J = 8.1 Hz, H-3′), 6.73 (t, 1H, J = 7.5 Hz, H-5′), 6.98−7.05 (m, 2H, H-4′, H-6′); ^{13}C NMR (400 MHz; $CDCl_3$) δ 21.3, 23.6, 28.9, 35.0, 43.5, 50.8, 55.2, 109.6, 119.8, 122.6, 127.6, 129.4, 130.4, 134.8, 157.2, 174.8; MS m/e (rel intensity) 91 (25), 93 (17), 115 (18), 121 (34), 128 (17), 143 (20), 144 (20), 152 (33), 159 (75), 169 (13), 173 (20), 174 (21), 185 (34), 200 (100), 201 (32), 260 (M^+, 27). Anal. Calcd for $C_{16}H_{20}O_3$: C, 73.82; H, 7.74. Found: C, 73.65; H, 7.80.

***rel*-1-((1*S*,2*R*)-2-(2′,4′-Dimethoxyphenyl)-4-methylcyclohex-3-enyl)ethanone (7bx).** Oil; IR ($CHCl_3$) 1705 (C═O) cm^{-1}; ^{1}H NMR (400 MHz; $CDCl_3$) δ 1.47 (m, 1H, J = 13.7, 6.4, 3.2 Hz, H-6β), 1.67 (s, 3H, CH_3), 1.68 (ddd, 1H, J = 10.8, 6.4, 2.7 Hz, H-6α), 1.88−2.00 (d broad, 1H, H-5β), 1.94 (s, 3H, CH_3C═O), 2.02 (dd broad 1H, J = 16.4, 6.4 Hz, H-5α), 2.83 (ddd, 1H, J = 12.3, 5.4, 2.6 Hz, H-1), 3.62 (s, 3H, OCH_3), 3.67 (s, 3H, OCH_3), 4.12 (s broad, 1H, H-2), 5.29 (s broad, 1H, H-3), 6.27 (s, 1H, H-3′), 6.32 (d, 1H, J = 8.4 Hz, H-5′), 6.93 (d, 1H, J = 8.4 Hz, H-6′); ^{13}C NMR (400 MHz; $CDCl_3$) δ 19.7, 23.5, 29.6, 29.8, 34.5, 51.6, 54.6, 55.2, 97.8, 103.5, 121.0, 123.1, 131.2, 134.7, 157.6, 159.5, 211.0; MS m/e (rel intensity) 43 (27), 77 (15), 91 (16), 115 (16), 121 (20), 138 (68), 151 (96), 158 (21), 173 (33), 174 (19), 189 (100), 190 (25), 203 (100), 204 (79), 231 (58), 274 (M^+, 49). Anal. Calcd for $C_{17}H_{22}O_3$: C, 74.42; H, 8.08. Found: C, 74.50; H, 8.10.

***rel*-(1*S*,2*R*)-Methyl 2-(2′,4′-Dimethoxyphenyl)-4-methylcyclohex-3-enecarboxylate (7by).** White solid, mp 107−108 °C (*n*-hexane); IR ($CHCl_3$) 1731 (C═O) cm^{-1}; ^{1}H NMR (400 MHz; $CDCl_3$) δ 1.61 (m, 1H, J = 13.6, 6.2, 3.2 Hz, H-6β), 1.68 (s, 3H, CH_3), 1.78 (m, 1H, H-6α), 1.95 (m, 1H, H-5β), 2.05 (dd broad, 1H, J = 17.5 Hz H-5α), 2.79 (ddd, 1H, J = 11.3, 5.7, 3.0 Hz, H-1), 3.36 (s, 3H, CH_3OC═O), 3.66 (s, 3H, OCH_3), 3.69 (s, 3H, OCH_3), 4.08 (s broad, 1H, H-2), 5.27 (s broad, 1H, H-3), 6.29 (s, 1H, H-3′), 6.33 (d, 1H, J = 8.4 Hz, H-5′), 6.95 (d, 1H, J = 8.4 Hz, H-6′); ^{13}C NMR (400 MHz; $CDCl_3$) δ 21.0, 23.6, 29.0, 34.5, 43.6, 50.9, 55.1, 55.2, 97.8, 103.3, 121.6, 122.9, 130.9, 134.5, 158.1, 159.4, 174.9; MS m/e (rel intensity) 115 (11), 138 (62), 151 (14), 158 (11), 165 (18), 173 (19), 189 (100), 190 (13), 203 (65), 204 (47), 215 (15), 230 (43), 290 (M^+, 32). Anal. Calcd for $C_{17}H_{22}O_4$: C, 70.32; H, 7.64. Found: C, 70.40; H, 7.69.

***rel*-1-((1*S*,2*R*)-2-(2′,6′-Dimethoxyphenyl)-4-methylcyclohex-3-enyl)ethanone (7cx).** Oil; IR ($CHCl_3$) 1702 (C═O) cm^{-1}; ^{1}H NMR (400 MHz; $CDCl_3$) δ 1.54 (s, 3H, CH_3), 1.56 (m, 1H, J = 6.8, 3.6 Hz, H-6β), 1.70 (s, 3H, CH_3C═O), 1.84 (m, 1H, H-5α), 1.98 (dd broad, 1H, H-5β), 2.09 (m, 1H, J = 11.7, 5.9, 3.3 Hz, H-6α), 2.78 (ddd, 1H, J = 11.3, 7.7, 3.6 Hz, H-1), 3.56 (s, 6H, OCH_3, OCH_3), 4.39 (d broad, 1H, H-2), 5.14 (s, 1H, H-3), 6.33 (d, 2H, J = 8.3 Hz, H-3′, H-5′), 6.95 (t, 1H, J = 8.3 Hz, H-4′); ^{13}C NMR (400 MHz; $CDCl_3$) δ 21.8 (C-6), 23.8 (4-CH_3), 29.0 (C-5), 29.1 (CH_3C═O), 32.0 (C-2), 51.4 (C-1), 55.5 (2′-OCH_3, 6′-OCH_3), 104.5 (C-3′, C-5′), 118.3 (C-1′), 122.5 (C-3), 127.9 (C-4′), 132.4 (C-4), 158.8 (C-2′, C-6′), 211.0 (C═O); MS m/e (rel intensity) 43 (19), 91 (25), 138 (100), 139 (20), 151 (100), 152 (20), 158 (28), 173 (82), 204 (27), 231 (35), 274 (M^+, 10). Anal. Calcd for $C_{17}H_{22}O_3$: C, 74.42; H, 8.08. Found: C, 74.35; H, 8.12.

***rel*-(1*S*,2*R*)-Methyl 2-(2′,6′-Dimethoxyphenyl)-4-methylcyclohex-3-enecarboxylate (7cy).** Oil; IR ($CHCl_3$) 1727 (C═O) cm^{-1}; ^{1}H NMR (400 MHz; $CDCl_3$) δ 1.62 (s, 3H, CH_3), 1.73 (m, 1H, J = 10.4, 7.9, 4.1 Hz, H-6β), 1.91 (m, 1H, H-5α), 2.12−2.22 (m, 2H, H-6α, H-5β), 2.80 (m, 1H, J = 11.4, 7.5, 3.6 Hz, H-1), 3.23 (s, 3H, CH_3OC═O), 3.64 (s, 6H, OCH_3, OCH_3), 4.35 (s broad, 1H, H-2), 5.24 (s broad, 1H, H-3), 6.41 (d, 2H, J = 8.2 Hz, H-3′, H-5′), 7.03 (t, 1H, J = 8.3 Hz, H-4′); ^{13}C NMR (400 MHz; $CDCl_3$) δ 23.0, 23.8, 28.4, 32.7, 42.8, 50.6, 55.7 (2C), 104.3 (2C), 118.8, 122.6, 127.6, 131.6, 159.0 (2C), 175.0; MS m/e (rel intensity) 91 (19), 115 (13), 138 (100), 139 (20), 151 (28), 158 (20), 165 (16), 173 (56), 204 (17), 215 (16), 230 (39), 290 (M^+, 2). Anal. Calcd for $C_{17}H_{22}O_4$: C, 70.32; H, 7.64. Found: C, 70.25; H, 7.71.

***rel*-1-((1*S*,2*R*)-2-(2′,6′-Dimethoxy-4′-pentylphenyl)-4-methylcyclohex-3-enyl)ethanone (7dx).** Oil; IR ($CHCl_3$) 1702 (C═O) cm^{-1}; ^{1}H NMR (400 MHz; $CDCl_3$) δ 0.80 (t, 3H, J = 6.9 Hz, CH_3), 1.14−1.28 (m, 4H, CH_2CH_2), 1.45−1.53 (m, 2H, CH_2), 1.60 (m, 1H, J = 6.5, 3.3 Hz, H-6β), 1.61 (s, 3H, CH_3), 1.77 (s, 3H, CH_3C═O), 1.94 (m, 1H, H-5α), 2.03 (dd broad, 1H, H-5β), 2.17 (ddd, 1H, J = 10.2, 5.9, 2.6 Hz, H-6α), 2.42 (t, 2H, J = 7.9 Hz, CH_2), 2.82 (ddd, 1H, J = 10.9, 7.6, 3.5 Hz, H-1), 3.62 (s, 6H, OCH_3, OCH_3), 4.42 (s broad, 1H, H-2), 5.21 (s, 1H, H-3), 6.22 (s, 2H, H-3′, H-5′); ^{13}C NMR (400 MHz; $CDCl_3$) δ 14.0 (C-5″), 21.7 (C-4″), 22.5 (C-6), 23.8 (4-CH_3), 29.0 (CH_3C═O), 29.1 (C-5), 30.9 (C-2″), 31.6 (C-3″), 31.9 (C-2), 36.4 (C-1″), 51.5 (C-1), 55.5 (2′-OCH_3, 6′-OCH_3), 104.7 (C-3′, C-5′), 115.4 (C-1′), 122.8 (C-3), 132.2 (C-4′), 143.0 (C-4), 158.5 (C-2′, C-6′), 211.1 (C═O); MS m/e (rel intensity) 43 (15), 152 (35), 173 (25), 208 (100), 209 (19), 221 (95), 222(15), 243 (41), 274 (54), 301 (28), 313 (15), 344 (M^+, 5).

dx.doi.org/10.1021/jo200796b |*J. Org. Chem.* 2011, 76, 5392–5403

Anal. Calcd for $C_{22}H_{32}O_3$: C, 76.70; H, 9.36. Found: C, 76.55; H, 9.45.

***rel*-(1*S*,2*R*)-Methyl 2-(2′,6′-Dimethoxy-4′-pentylphenyl)-4-methylcyclohex-3-enecarboxylate (7dy).** White solid, mp 29−30 °C (*n*-hexane); IR ($CHCl_3$) 1728 (C═O) cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 0.80 (t, 3H, J = 7.0 Hz, CH_3), 1.19−1.27 (m, 4H, CH_2CH_2), 1.46−1.56 (m, 2H, CH_2), 1.57 (m, 1H, H-6β), 1.61 (s, 3H, CH_3), 1.71 (m, 1H, H-5α), 1.89 (m, 1H, H-5β), 2.17 (m, 1H, H-6α), 2.44 (t, 2H, J = 7.8 Hz, CH_2), 2.78 (ddd, 1H, J = 11.0, 7.5, 3.6 Hz, H-1), 3.23 (s, 3H, CH_3OC═O), 3.63 (s, 6H, OCH_3, OCH_3), 4.30 (s broad, 1H, H-2), 5.23 (s, 1H, H-3), 6.23 (s, 2H, H-3′, H-5′); ^{13}C NMR (400 MHz; $CDCl_3$) δ 14.1, 22.5, 22.9, 23.8, 28.4, 31.0, 31.6, 32.6, 36.4, 42.9, 50.6, 55.7 (2C), 104.5 (2C), 115.8, 131.5, 142.7, 158.7, 175.1; MS m/e (rel intensity) 152 (36), 173 (23), 208 (100), 209 (23), 221 (18), 235 (16), 243 (40), 274 (46), 300 (79), 301 (18), 360 (M^+, 4). Anal. Calcd for $C_{22}H_{32}O_4$: C, 73.30; H, 8.95. Found: C, 73.35; H, 8.89.

Epimerization of *endo*-Adducts 7 to *exo*-Adducts 8. A solution of 0.56 mmol of *endo*-adduct **7** in absolute methanol (1 mL) was added to a 1 M freshly prepared solution (2 mL) of sodium methoxide in dry methanol under nitrogen. The mixture was stirred at the indicated temperature for the time needed to establish equilibrium (as monitored by GC analysis) (Table 3). Next, the reaction mixture was quenched with dilute HCl, taken up in 25 mL of ether, and washed with saturated aqueous NaCl. The dried extract (Na_2SO_4) was concentrated under vacuum and chromatographed over silica gel. Elution with 10% to 20% diethyl ether/petroleum ether gave cycloadducts **8**.

***rel*-1-((1*R*,2*R*)-2-(2′-Methoxyphenyl)-4-methylcyclohex-3-enyl)ethanone (8ax).** Light yellow oil; IR ($CHCl_3$) 1703 (C═O) cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 1.57 (s, 3H, CH_3), 1.62 (m, 1H, J = 9.6, 6.0, 3.6 Hz H-6β), 1.71 (ddd, 1H, J = 13.2, 6.5, 2.0 Hz, H-6α), 1.86−1.91 (m, 2H, H-5α, H-5β), 1.91 (s, 3H, CH_3C═O), 2.51 (ddd, 1H, J = 9.7, 6.7, 3.6 Hz, H-1), 3.64 (s, 3H, OCH_3), 3.97 (s broad, 1H, H-2), 5.14 (s broad, 1H, H-3), 6.68 (d, 1H, J = 8.2 Hz, H-3′), 6.75 (t, 1H, J = 7.5 Hz, H-5′), 6.98−7.03 (m, 2H, H-4′, H-6′); ^{13}C NMR (400 MHz; $CDCl_3$) δ 23.4, 23.6, 28.2, 28.3, 36.1, 53.1, 55.3, 110.3, 120.4, 123.0, 127.4, 128.8, 132.7, 134.4, 156.8, 211.5; MS m/e (rel intensity) 67 (41), 77 (17), 82 (100), 91 (19), 115 (16), 118 (51), 146 (68), 147 (90), 185 (16), 228 (80), 229 (23), 244 (M^+, 3). Anal. Calcd for $C_{16}H_{20}O_2$: C, 78.65; H, 8.25. Found: C, 78.48; H, 8.19.

***rel*-(1*R*,2*R*)-Methyl 2-(2′-Methoxyphenyl)-4-methylcyclohex-3-enecarboxylate (8ay).** Oil; IR ($CHCl_3$) 1727 (C═O) cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 1.57 (s, 3H, CH_3), 1.66−1.81 (m, 2H, H-6α, H-6β), 1.83−1.94 (m, 2H, H-5α, H-5β), 2.51 (ddd, 1H, J = 10.7, 7.1, 3.6 Hz, H-1), 3.43 (s, 3H, CH_3OC═O), 3.65 (s, 3H, OCH_3), 4.00 (s broad, 1H, H-2), 5.13 (s broad, 1H, H-3), 6.68 (d, 1H, J = 8.1 Hz, H-3′), 6.74 (t, 1H, J = 7.5 Hz, H-5′), 6.97−7.05 (m, 2H, H-4′, H-6′); ^{13}C NMR (400 MHz; $CDCl_3$) δ 23.6, 24.2, 28.4, 36.9, 45.0, 51.4, 55.4, 110.4, 120.3, 123.2, 127.4, 128.8, 132.5, 134.0, 157.1, 175.8; MS m/e (rel intensity) 91 (18), 121 (22), 159 (32), 185 (31), 200 (100), 201 (23), 260 (M^+, 14). Anal. Calcd for $C_{16}H_{20}O_3$: C, 73.82; H, 7.74. Found: C, 73.92; H, 7.69.

***rel*-1-((1*R*,2*R*)-2-(2′,4′-Dimethoxyphenyl)-4-methylcyclohex-3-enyl)ethanone (8bx).** Oil; IR ($CHCl_3$) 1704 (C═O) cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 1.63 (s, 3H, CH_3), 1.65−1.71 (m, 1H, H-6β), 1.73−1.82 (m, 1H, H-6α), 1.89 (m, 2H, H-5α, H5β), 1.97 (s, 3H, CH_3C═O), 2.53 (ddd broad, 1H, J = 10.4, 6.9, 3.6 Hz, H-1), 3.68 (s, 3H, OCH_3), 3.69 (s, 3H, OCH_3), 3.92 (s broad, 1H, H-2), 5.18 (s broad, 1H, H-3), 6.34 (s, 1H, H-3′), 6.35 (d, 1H, J = 7.5 Hz, H-5′), 6.94 (d, 1H, J = 7.2 Hz, H-6′); ^{13}C NMR (400 MHz; $CDCl_3$) δ 23.5, 23.6, 28.3, 28.4, 53.4, 55.3 (2C), 98.4, 104.0, 123.4, 125.1, 129.2, 134.1, 157.7, 159.3, 211.7; MS m/e (rel intensity) 43 (19), 121 (20), 138 (48), 151 (72), 173 (20), 189 (100), 190 (17), 203 (63), 204 (61), 231 (68), 243 (15), 274 (M^+, 88). Anal. Calcd for $C_{17}H_{22}O_3$: C, 74.42; H, 8.08. Found: C, 74.35; H, 8.02.

***rel*-(1*R*,2*R*)-Methyl 2-(2′,4′-Dimethoxyphenyl)-4-methylcyclohex-3-enecarboxylate (8by).** Oil; IR ($CHCl_3$) 1727 (C═O) cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 1.56 (s, 3H, CH_3), 1.66−1.78 (m, 2H, H-6α, H-6β), 1.78−1.96 (m, 2H, H-5α, H-5β), 2.46 (m, 1H, H-1), 3.43 (s, 3H, CH_3OC═O), 3.62 (s, 3H, OCH_3), 3.63 (s, 3H, OCH_3), 3.90 (s broad, 1H, H-2), 5.12 (s, 1H, H-3), 6.27 (s broad, 2H, H-3′, H-5′), 6.87 (d, 1H, J = 8.9 Hz, H-6′); ^{13}C NMR (400 MHz; $CDCl_3$) δ 23.6, 24.2, 28.4, 36.5, 45.2, 51.4, 55.2, 55.4, 98.4, 103.8, 115.7, 123.5, 124.9, 129.1, 133.8, 157.9, 159.3, 175.8; MS m/e (rel intensity) 77 (13), 91 (14), 115 (18), 128 (14), 138 (41), 139 (10), 151 (26), 158 (14), 165 (20), 173 (21), 174 (12), 189 (100), 190 (14), 203 (62), 204 (48), 215 (37), 230 (87), 231 (19), 290 (M^+, 61). Anal. Calcd for $C_{17}H_{22}O_4$: C, 70.32; H, 7.64. Found: C, 70.25; H, 7.70.

***rel*-1-((1*R*,2*R*)-2-(2′,6′-Dimethoxyphenyl)-4-methylcyclohex-3-enyl)ethanone (8cx).** Light yellow oil; IR ($CHCl_3$) 1702 (C═O) cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 1.51 (s, 3H, CH_3), 1.65 (dd, 1H, J = 12.5, 11.0, 5.0 Hz, H-6β), 1.73 (s, 3H, CH_3C═O), 1.73−1.78 (m, 1H, H-6α), 1.85 (dd broad, 1H, J = 16.9, 5.0 Hz, H-5β), 1.95−2.03 (m, 1H, H-5α), 3.14 (ddd, 1H, J = 10.6, 9.6, 3.5 Hz, H-1), 3.60 (s, 6H, OCH_3, OCH_3), 4.06 (d broad, 1H, J = 9.4 Hz, H-2), 4.99 (s, 1H, H-3), 6.36 (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 23.3 (4-CH_3), 26.5 (C-6), 28.6 (CH_3C═O), 29.5 (C-5), 34.7 (C-2), 50.9 (C-1), 55.9 (2′-OCH_3, 6′-OCH_3), 104.7 (C-3′, C-5′), 120.0 (C-1′), 124.5 (C-3), 127.6 (C-4′), 131.2 (C-4), 158.7 (C-2′, C-6′), 213.3 (C═O); MS m/e (rel intensity) 43(22), 91 (28), 121 (21), 138 (100), 151 (100), 173 (50), 231 (43), 243 (33), 274 (M^+, 31). Anal. Calcd for $C_{17}H_{22}O_3$: C, 74.42; H, 8.08. Found: C, 74.58; H, 8.15.

***rel*-(1*R*,2*R*)-Methyl 2-(2′,6′-Dimethoxyphenyl)-4-methylcyclohex-3-enecarboxylate (8cy).** Oil; IR ($CHCl_3$) 1727 (C═O) cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 1.57 (s, 3H, CH_3), 1.80 (ddd, 1H, J = 12.5, 10.2, 5.2 Hz, H-6β), 1.85−1.98 (m, 1H, H-6α), 2.05−2.20 (m, 2H, H-5α, H-5β), 3.1 (ddd, 1H, J = 10.2, 9.6, 3.5 Hz, H-1), 3.37 (s, 3H, CH_3OC═O), 3.67 (s, 6H, OCH_3, OCH_3), 4.20 (d broad, 1H, J = 9.1 Hz, H-2), 5.06 (s, 1H, H-3), 6.43 (d, 2H, J = 8.3 Hz, H-3′, H-5′), 7.03 (t, 1H, J = 8.3 Hz, H-4′); ^{13}C NMR (400 MHz; $CDCl_3$) δ 23.3, 27.1, 29.4, 34.9, 43.2, 51.1, 56.0 (2C), 104.7 (2C), 120.3, 124.3, 127.4, 131.1, 158.9 (2C), 176.6; MS m/e (rel intensity) 91 (15), 138 (41), 151 (33), 165 (15), 173 (33), 215 (28), 230 (100), 231 (18), 290 (M^+, 13). Anal. Calcd for $C_{17}H_{22}O_4$: C, 70.32; H, 7.64. Found: C, 70.43; H, 7.58.

***rel*-1-((1*R*,2*R*)-2-(2′,6′-Dimethoxy-4′-pentylphenyl)-4-methylcyclohex-3-enyl)ethanone (8dx).** Oil; IR ($CHCl_3$) 1702 (C═O) cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 0.80 (t, 3H, J = 7.0 Hz, CH_3-), 1.14−1.29 (m, 4H, CH_2CH_2), 1.46−1.58 (m, 2H, CH_2), 1.57 (s, 3H, CH_3), 1.64−1.77 (m, 1H, H-6β), 1.77−1.85 (m, 1H, H-6α), 1.80 (s, 3H, CH_3C═O), 1.89 (dd broad, 1H, H-5β), 2.00−2.08 (m, 1H, H-5α), 2.43 (t, 2H, J = 7.7 Hz, CH_2), 3.18 (ddd broad, 1H, J = 11.2, 9.7, 3.0 Hz, H-1), 3.65 (s, 6H, OCH_3, OCH_3), 4.07 (d broad, 1H, H-2), 5.06 (s, 1H, H-3), 6.25 (s, 2H, H-3′, H-5′); ^{13}C NMR (400 MHz; $CDCl_3$) δ 14.0 (C-5″), 22.5 (C-4″), 23.3 (4-CH_3), 26.5 (C-6), 28.6 (CH_3C═O), 29.5 (C-5), 31.0 (C-2″), 31.6 (C-3″), 34.6 (C-2), 36.4 (C-1″), 51.1 (C-1), 55.9 (2′-OCH_3, 6′-OCH_3), 104.9 (C-3′, C-5′), 117.2 (C-1′), 124.8 (C-3), 131.0 (C-4′), 142.8 (C-4), 158.4 (C-2′, C-6′), 213.6 (C═O); MS m/e (rel intensity) 43 (17), 152 (36), 166 (11), 173 (26), 208 (100), 209 (19), 221 (97), 222 (16), 243 (42), 274 (56), 301 (29), 344 (M^+, 5). Anal. Calcd for $C_{22}H_{32}O_3$: C, 76.70; H, 9.36. Found: C, 76.61; H, 9.30.

***rel*-(1*R*,2*R*)-Methyl 2-(2′,6′-Dimethoxy-4′-pentylphenyl)-4-methylcyclohex-3-enecarboxylate (8dy)[7m].** White solid, mp 89−90 °C (*n*-hexane); IR ($CHCl_3$) 1736 (C═O) cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 0.90 (t, 3H, J = 7.0 Hz, CH_3-), 1.26−1.39 (m, 4H, CH_2CH_2), 1.52−1.64 (m, 2H, CH_2), 1.63−1.73 (m, 1H, H-6 β), 1.64 (s, 3H, CH_3), 1.84−1.96 (m, 2H, H-6α, H-5β), 2.05−2.13 (m, 1H, H-5α), 2.50 (t, 2H, J = 7.9 Hz, CH_2), 3.04 (ddd, 1H, J = 11.7, 10.7, 2.4 Hz, H-1), 3.22 (s, 3H, CH_3OC═O), 3.60 (s, 6H, OCH_3, OCH_3), 4.06

dx.doi.org/10.1021/jo200796b |*J. Org. Chem.* 2011, 76, 5392–5403

(d broad, 1H, J = 9.7 Hz, H-2), 5.08 (s, 1H, H-3), 6.30 (s, 2H, H-3′, H-5′); ^{13}C NMR (400 MHz; $CDCl_3$) δ 14.1, 22.6, 23.4, 27.8, 29.8, 31.0, 31.8, 34.9, 36.4, 44.4, 50.6, 56.6, 106.1, 119.0, 124.9, 130.9, 142.2, 158.7, 182.4; MS m/e (rel intensity) 43 (19), 57 (19), 71 (15), 149 (83), 152 (27), 167 (37), 208 (42), 221 (49), 243 (22), 285 (27), 300 (100), 301 (35), 360 (M^+, 41). Anal. Calcd for $C_{22}H_{32}O_4$: C, 73.30; H, 8.95. Found: C, 73.40; H, 8.81.

Procedure for Preparing Δ^9-*cis*-THC 1. According to the procedure described previously for the synthesis of Δ^8-*trans*-THC,[1e] to a solution of ketone **7dx** (0.20 g, 0.58 mmol) in toluene (40 mL) was slowly added a 3.0 M solution of CH_3MgBr in ether (1.9 mL, 5.8 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 dried extract (Na_2SO_4) was concentrated under vacuum and purified by flash silica gel column chromatography (petroleum ether/diethyl ether, 4:1) to give the alcohol **11** (0.198 g, 0.55 mmol, 95%).

Next, a mixture of alcohol **11** (0.145 g, 0.4 mmol) and NaSMe (1.2 mmol) dissolved in DMF (4 mL) was stirred at 140 °C for 3 h. This was then cooled to room temperature, poured into saturated aqueous $NaHCO_3$ and extracted twice with diethyl ether. The dried extract (Na_2SO_4) was concentrated under vacuum and purified by silica gel column chromatography (20% ethyl acetate/petroleum ether) to yield 0.118 g (85%) of pure **12**. Then, a solution of **12** (0.107 g, 0.31 mmol) in benzene (30 mL) with a few crystals of TsOH (0.003 mmol, 1 mg) was stirred at 75 °C for 0.5 h.[15] After cooling to room temperature, the mixture was poured into saturated aqueous $NaHCO_3$ and extracted with ethyl acetate (2 × 10 mL). The dried extract (Na_2SO_4) was concentrated under vacuum and purified by chromatography over neutral aluminum oxide, eluting with 3% ethyl acetate/petroleum ether to give the cyclyzed ether **13** (0.064 g, 0.195 mmol, 65%). Finally, a solution of ether **13** (0.059 g, 0.18 mmol) and NaSMe (1.8 mmol) in DMF (14 mL) was stirred at 140 °C for 14 h.[1e,7m] After cooling to room temperature, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ (20 mL) and extracted with diethyl ether (2 × 20 mL). The combined organic layers were washed with saturated aqueous NaCl, dried (Na_2SO_4), and concentrated under vacuum. The residue was purified by chromatography over silica gel, eluting with 5% ethyl acetate/petroleum ether to yield the desidered racemic Δ^9-*cis*-THC (**1**)[7a,d,g] (0.039 g, 0.126 mmol, 70%).

***rel*-2-((1*S*,2*R*)-2-(2′,6′-Dimethoxy-4′-pentylphenyl)-4-methylcyclohex-3-enyl)propan-2-ol (11).** Pale yellow oil, IR ($CHCl_3$) 3506 (OH) cm^{-1}; ^{1}H NMR (400 MHz; $CDCl_3$) δ 0.64 (s, 3H, CH_3COH), 0.89 (t, 3H, J = 6.9 Hz, CH_3), 1.15 (s, 3H, CH_3COH), 1.25−1.42 (m, 4H, CH_2CH_2), 1.52−1.66 (m, 2H, CH_2), 1.68 (s, 3H, CH_3), 1.90−2.01 (m, 2H, H-6α, H-5α), 2.01−2.15 (m, 2H, H-6β, H-5β), 2.55 (t, 2H, J = 7.8 Hz, CH_2), 3.67 (s, 3H, OCH_3), 3.77 (s broad, 1H, H-1), 3.86 (s, 3H, OCH_3), 4.14 (s broad, 1H, H-2), 5.24 (s broad, 1H, H-3), 6.37 (s, 2H, H-3′, H-5′); ^{13}C NMR (400 MHz; $CDCl_3$) δ 14.0, 22.5, 23.6, 24.5, 26.4, 30.2, 30.9, 31.4, 31.4, 31.5, 36.2, 50.7, 56.0, 56.0, 73.1, 104.5, 107.1, 117.4, 123.2, 132.6, 143.1, 156.6, 160.0; MS m/e (rel intensity) 43 (51), 59 (72), 71 (26), 173 (28), 221 (29), 243 (39), 274 (100), 275 (20) 311 (19), 342 (26), 360 (M^+, 1). Anal. Calcd for $C_{23}H_{36}O_3$: C, 76.62; H, 10.06. Found: C, 76.68; H, 9.98.

***rel*-2-((1*S*,2*R*)-2-(2′-Hydroxy-6′-methoxy-4′-pentylphenyl)-4-methylcyclohex-3-enyl)propan-2-ol (12).** Oil; IR ($CHCl_3$) 3503 (OH) cm^{-1}; ^{1}H NMR (400 MHz; $CDCl_3$) δ 0.56 (s, 3H, CH_3COH), 0.87 (t, 3H, J = 7.0 Hz, CH_3), 1.19 (s, 3H, CH_3COH), 1.24−1.35 (m, 4H, CH_2CH_2), 1.54−1.62 (m, 2H, CH_2), 1.66−1.80 (m, 2H, H-6α, H-5α), 1. 79 (s, 3H, CH_3), 1.92−2.00 (m, 1H, H-1), 2.20−2.26 (m, 2H, H-6β, H-5β), 2.50 (t, 2H, J = 7.8 Hz, CH_2), 3.84 (s, 3H, OCH_3), 4.16 (s broad, 1H, H-2), 5.71 (s broad, 1H, H-3), 6.31 (s, 1H, H-3′), 6.35 (s, 1H, H-5′); ^{13}C NMR (400 MHz; $CDCl_3$) δ 14.0, 22.5, 22−8, 23.4, 23.6, 30.5, 30.7, 31.5, 32.0, 33.0, 35.7, 51.7, 56.0, 72.3, 103.6, 111.2, 111.8, 125.4, 139.0, 144.0, 156.2, 157.7; MS m/e (rel intensity) MS m/e (rel intensity) 43 (50), 59 (84), 71 (24), 207 (13), 245 (100), 246 (19), 260 (15), 285 (15), 347 (M^+, 2). Anal. Calcd for $C_{22}H_{34}O_3$: C, 76.26; H, 9.89. Found: C, 76.38; H, 9.94.

***rel*-(6a*S*,10a*R*)-6a,7,8,10a-Tetrahydro-1-methoxy-6,6,9-trimethyl-3-pentyl-6*H*-benzo[*c*]chromene (13).** Oil; IR ($CHCl_3$) 1615, 1575 cm^{-1}; ^{1}H NMR (400 MHz; $CDCl_3$) δ 0.90 (t, 3H, J = 7.0 Hz, CH_3), 1.28 (s, 3H, CH_3), 1.29−1.37 (m, 4H, CH_2CH_2), 1.39 (s, 3H, CH_3), 1,59 (m, 2H, CH_2), 1.67 (s, 3H, CH_3), 1.77−2.22 (m, 5H, H-7α, H-7β, H-8α, H-8β), 2.48−2.55 (m, 3H, H-6a, CH_2), 3.53(br s, 1H, H-10a), 3.80 (s, 3H, OCH_3), 5.35 (s, 1H, H-10), 6.25 (d, 1H, J = 1.2 Hz, H-4), 6.30 (s, 1H, H-2); ^{13}C NMR (400 MHz; $CDCl_3$) δ 14.0, 22.6, 22.9, 23.5, 25.3, 27.8, 29.6, 30.1, 30.9, 31.7, 36.1, 37.5, 40.1, 55.3, 78.0, 107.7, 109.7, 110.1, 118.7, 122.8, 133.0, 142.3, 153.3, 158.8; MS m/e (rel intensity) 43 (21), 67 (21), 68 (37), 174 (5), 188 (7), 245 (100), 246 (19), 260 (6), 328(M^+, 10). Anal. Calcd for $C_{22}H_{32}O_2$: C, 80.44; H, 9.82. Found: C, 80.55; H, 9.78.

***rel*-(6a*S*,10a*R*)-6a,7,8,10a-Tetrahydro-6,6,9-trimethyl-3-pentyl-6*H*-benzo[*c*]chromen-1-ol (1)[7a,d,g].** Colorless oil; IR ($CHCl_3$) 3007, 1623, 1580 cm^{-1}; ^{1}H NMR (400 MHz; $CDCl_3$) δ 0.88 (t, 3H, J = 6.9 Hz, CH_3), 1.25−1.33 (m, 4H, CH_2CH_2), 1.27 (s, 3H, CH_3), 1.38−1.41 (m, 2H, CH_2), 1.39 (s, 3H, CH_3), 1.54 (s, 3H, CH_3), 1.93−2.26 (m, 5H, H-7α, H-7β, H-8α, H-8β, H-6a), 2.45 (m, 2H, CH_2), 3.58(s broad, 1H, H-10a), 5.36 (s, 1H, OH), 6.12 (d, J = 1.2 Hz, H-4), 6.21 (d broad, 1H, J = 5.2 Hz, H-10), 6.26 (d, 1H, J = 1.2 Hz, H-2); ^{13}C NMR (400 MHz; $CDCl_3$) δ 14.0, 23.2, 23.6, 25.2, 25.4, 27.9, 30.7, 31.6, 33.1, 35.5, 37.6, 40.1, 78.0, 106.8, 109.8, 112.0, 118.9, 132.6, 135.0, 142.6, 154.1; MS m/e (rel intensity) 43 (20), 174 (26), 193 (11), 231 (100), 232 (44), 243 (21), 246 (18), 258 (17), 271 (34), 299 (52), 300 (11), 314 (M^+, 82). Anal. Calcd for $C_{21}H_{30}O_2$: C, 80.21; H, 9.62. Found: C, 80.25; H, 9.69.

Procedure for Preparing Δ^9-*trans*-THC 2. According to the procedure described above, a solution of ketone **8dx** (0.10 g, 0.29 mmol) in toluene (10 mL) and 1 mL of a 3.0 M solution of CH_3MgBr in ether (3 mmol) was heated at 60 °C for 1.5 h. After the usual workup, the resulting crude product and NaSMe (0.9 mmol) in DMF (3 mL) was heated at 140 °C for 3 h. After cooling and the usual workup, the resulting oil was purified by column chromatography on silica gel (elution with 10% ethyl acetate/petroleum ether) to yield the known diol **14**[7j,m,8d] (0.075 g, 0.22 mmol,75%). The subsequent conversion of **14** into **2** has been reported in literature.[7j,m]

SAMP-Hydrazones (*S*,*R*,*R*)-(+)-16 and (*S*,*S*,*S*)-(+)-16. According to the procedure we described previously[1e] for the resolution of Δ^8-THC, a solution of *rac*-**8dx** (0.290 g, 0.84 mmol), SAMP [*S*-(−)-**15**] (0.24 mL, 0.172 mmol), and a few crystals of p-TsOH in 1.8 mL of heptane was heated at 100 °C for 47 h. After cooling at room temperature, the reaction was diluted with Et_2O, washed with saturated aqueous $NaHCO_3$, and dried (Na_2SO_4). Evaporation of the solvent under vacuum gave a 1:1 mixture of two diastereoisomeric hydrazones **16**, which was chromatographed on silica gel (elution, 9:1 petroleum ether/diethyl ether) to give diastereomerically pure SAMP-hydrazones (*S*,*R*,*R*)-(+)-**16** (0.142 g, 0.31 mmol, 37%) and (*S*,*S*,*S*)-(+)-**16** (0.153 g, 0.34 mmol, 40%).

(2″*S*)-*N*-{(1*E*)-1-[(1*R*,2*R*)-2-(2′,6′-Dimethoxy-4′-pentylphenyl)-4-methylcyclohex-3-en-1-yl]ethylidene}-2″-(methoxymethyl)pyrrolidin-1″-amine (*S*,*R*,*R*)-(+)-16. Pale yellow oil; $[\alpha]_D$ = +54 (*c* 1.99, $CHCl_3$); IR ($CHCl_3$) 1608 (C=N) cm^{-1}; ^{1}H NMR (400 MHz; $CDCl_3$) δ 0.89 (t, 3H, J = 6.4 Hz, CH_3), 1.30−1.34 (m, 4H, CH_2CH_2), 1.473−1.61 (m, 3H, CH_2, H-3″), 1.66 (s, 3H, 4-CH_3), 1.75 (s, 3H, CH_3, C=N), 1.70−1.91 (m, 4H, H-5, H-6, H-3″, H4″), 1.97 (d broad, 1H, J = 15.3 Hz, H-5), 2.13−2.31 (m, 2H, H-6, H-5″), 2.50 (t, 2H, J = 8.0 Hz, CH_2), 2.72 (dd, 1H, J = 9.2, 7.2 Hz, OCH_2), 2.83 (dd, 1H, J = 9.5, 3.2 Hz, OCH_2), 2.87 (d broad, 1H, J = 7.2 Hz, H-2″), 2.94−2.99 (m, 1H, H-5″), 3.10 (ddd, 1H, J = 11.2, 11.2, 5.2 Hz, H-1),

dx.doi.org/10.1021/jo200796b |*J. Org. Chem.* 2011, 76, 5392–5403

3.14 (s, 3H, OCH_3), 3.71 (s, 6H, 2′-OCH_3, 6′-OCH_3), 4.09 (d broad, 1H, J = 10.9 Hz, H-2), 5.21 (s broad, 1H, H-3), 6.31 (s, 2H, H-3′, H-5′); ^{13}C NMR (400 MHz, $CDCl_3$) δ 13.9,14.0, 21.8, 22.0, 23.4, 26.2, 27.9, 29.9, 31.2, 31.7, 35.1, 36.5, 45.3, 53.7, 55.7, 58.9, 58.9, 65.9, 74.5, 104.9, 117.5, 125.3, 130.9, 142.1, 159.2, 160.5, 170.4; MS m/e (rel.int.) 43 (22), 45 (43), 55 (14), 68 (30), 70 (41), 137 (100), 173 (9), 221 (22), 300 (7), 411 (44), 456 (M^+, 8). Anal. Calcd for $C_{28}H_{44}N_2O_3$: C, 73.64; H, 9.71; N, 6.13. Found: C, 73.71; H, 9.75; N, 6.07.

(2″*S*)-*N*-{1-[(1*S*,2*S*)-2-(2′,6′-Dimethoxy-4′-pentylphenyl)-4-methylcyclohex-3-en-1-yl]ethylidene}-2″-(methoxymethyl)-pyrrolidin-1″-amine (*S*,*S*,*S*)-(+)-16. Pale yellow oil; $[\alpha]_D$ = +156 (c 1.25, $CHCl_3$); IR ($CHCl_3$) 1608 (C=N) cm^{-1}; ^{1}H NMR (400 MHz; $CDCl_3$) δ 0.89 (t, 3H, J = 6.9 Hz, CH_3), 1.28−1.33 (m, 5H, H-4″, CH_2CH_2), 1.49−1.63 (m, 4H, CH_2, H-5″, H-3″), 1.66 (s, 5H, H-6, H-4″, 4-CH_3), 1.75 (s, 3H, CH_3, C=N), 1.80−1.84 (m, 2H, H-6, H-3″), 1.98 (d broad, 2H, J = 16.4 Hz, H-5″, H-5), 2.20 (s broad, 1H, H-5”), 2.50 (t, 2H, J = 8.0 Hz, CH_2), 2.68 (s broad, 1H, H-5), 3.04−3.15 (m, 3H, H-1, H-2″,OCH_2), 3.27 (s, 3H, OCH_3), 3.28 (m, 1H, OCH_2), 3.72 (s, 6H, 2′-OCH_3, 6′-OCH_3), 4.10 (d broad, 1H, H-2), 5.22 (s broad, 1H, H-3), 6.29 (s, 2H, H-3′, H-5′); ^{13}C NMR (400 MHz, $CDCl_3$) δ 14.0, 21.9, 22.5, 23.4, 26.7, 27.9, 30.1, 31.2, 31.5, 35.4, 36.4, 46.0, 53.6, 55.8, 55.9, 59.0, 65.8, 75.4, 104.9, 117.6, 125.4, 131.1, 142.2, 153.5, 155.2, 169.4; MS m/e (rel.int.) 43 (23), 45 (44), 68 (23), 70 (43), 71 (15), 137 (100), 173 (10), 221 (18), 300 (6), 411 (25), 456 (M^+, 7). Anal. Calcd for $C_{28}H_{44}N_2O_3$: C, 73.64; H, 9.71; N, 6.13. Found: C, 73.85; H, 9.68; N, 6.07.

Hydrolysis of the SAMP-Hydrazones (*S*,*R*,*R*)-(+)-16 and (*S*,*S*,*S*)-(+)-16 and Synthesis of (*R*,*R*)-(−)- and (*S*,*S*)-(+)-Δ^9-THCs (2). An aqueous saturated solution of oxalic acid (0.6 mL) was added to a solution of (*S*,*R*,*R*)-(+)-**16** (0.142 g, 0.31 mmol) in diethyl ether (4 mL).[1e] 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 95:5 petroleum ether/diethyl ether afforded 80 mg (75%) of pure (*R*,*R*)-(−)-**8dx** $[\alpha]_D$ = −98 (c 2.28, $CHCl_3$).

Similarly, hydrolysis of (*S*,*S*,*S*)-(+)-**16** (0.153 g, 0.34 mmol) gave 76 mg (65%) of pure (*S*,*S*)-(+)-**8dx** $[\alpha]_D$ = +101 (c 1.68, $CHCl_3$).

The procedure described for the synthesis of racemic Δ^9-THC **2** (see above) was repeated with enantiomerical pure cyloadducts (*R*,*R*)-(−)-**8dx** and (*S*,*S*)-(+)-**8dx** to provide (*R*,*R*)-(−)-**2** $[\alpha]_D$ = −148 (c 0.35, $CHCl_3$) (lit.[7m] $[\alpha]_D$ = −152 (c 0.46, $CHCl_3$)) and (*S*,*S*)-(+)-Δ^9-THC **2** $[\alpha]_D$ = +143 (c 0.39, $CHCl_3$) (lit.[8c] $[\alpha]_D$ = +141 (c 0.55, $CHCl_3$)), respectively, through the key intermediate diols (*R*,*R*)-(−)-**14** $[\alpha]_D$ = −48 (c 1.45, $CHCl_3$) (lit[7m] $[\alpha]_D$ = −52 (c 0.79, $CHCl_3$)) and (*S*,*S*)-(+)-**14** ($[\alpha]_D$ = +46 (c 0.92, $CHCl_3$)).

■ ASSOCIATED CONTENT

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

■ AUTHOR INFORMATION

Corresponding Author
*E-mail: lucio@unipg.it.

■ ACKNOWLEDGMENT

The authors thank the Fondazione Cassa Risparmio Perugia and the Ministero dell'Istruzione dell'Università e della Ricerca (MIUR) for financial support.

■ REFERENCES

(1) (a) Minuti, L.; Marrocchi, A.; Tesei, I.; Gacs-Baitz, E. *Tetrahedron Lett.* **2005**, *46*, 8789–8792. (b) Girotti, R.; Marrocchi, A.; Minuti, L.; Piermatti, O.; Pizzo, F.; Vaccaro, L. *J. Org. Chem.* **2006**, *71*, 70–74. (c) Minuti, L.; Marrocchi, A.; Landi, S.; Seri, M.; Gacs-Baitz, E. *Tetrahedron* **2007**, *63*, 5477–5481. (d) Ballerini, E.; Minuti, L.; Piermatti, O.; Pizzo, F. *J. Org. Chem.* **2009**, *74*, 4311–4317. (e) Ballerini, E.; Minuti, L.; Piermatti, O. *J. Org. Chem.* **2010**, *75*, 4251–4260.

(2) Nicolaou, K. C.; Pfefferkorn, J. A.; Roecker, A. J.; Cao, G.-Q.; Barluenga, S.; Mitchell, H. J. *J. Am. Chem. Soc.* **2000**, *122*, 9939–9953.

(3) (a) Matsuda, L. A.; Lolait, S. J.; Brownstein, M. J.; Young, A. C.; Bonner, T. I. *Nature* **1990**, *346*, 561–564. (b) Devane, W. A.; Hanus, L.; Breuer, A.; Pertwee, R. G.; Stevenson, L. A.; Griffin, G.; Gibson, D.; Mandelbaum, A.; Etinger, A.; Mechoulam, R. *Science* **1992**, *258*, 1946–1949. (c) Munro, S.; Thomas, K. L.; Abu-Shaar, M. *Nature* **1993**, *365*, 61–65. (d) Mechoulam, R.; Parker, L. A.; Gallily, R. J. *J. Clin. Pharmacol.* **2002**, *42*, 11S–19. (e) Choi, Y. H.; Hazekamp, A.; Peltenburg-Looman, A. M. G.; Frederich, M.; Erkelens, C.; Lefeber, A. W. M.; Verpoorte, R. *Phytochem. Anal.* **2004**, *15*, 345–354. (f) ElSoly, M. A. *Life Sci.* **2005**, 539–548. (g) Radwan, M. M.; Ross, S. A.; Slade, D.; Ahmed, S. A.; Zulfiqar, F.; ElSoly, M. A. *Planta Med.* **2008**, *74*, 267–272.

(4) (a) *Cannabinoids as Therapeutic Agents*; Mechoulam, R. Ed.; CRC Press: Boca Raton, FL, 1986. (b) Howlett, A. C. *Neuropharmacology* **1987**, *26*, 507–512. (c) Devane, W. A.; Dysarz, F. A.; Johnson, M. R.; Melvin, L. S.; Howlett, A. C. *Mol. Pharmacol.* **1988**, *34*, 605–613. (d) Compton, D. R.; Prescott, W. R.; Martin, B. R.; Siegel, C.; Gordo, P. M.; Razdan, R. K. *J. Med. Chem.* **1991**, *34*, 3310–3316. (e) Di Marzo, V.; Breivigel, C. S.; Tao, Q.; Bridgen, D. T.; Razdan, R. K.; Zimmer, A. M.; Zimmer, A.; Martin, B. R. *J. Neurochem.* **2000**, *75*, 2434–2444. (f) Howlett, A. C.; Barth, F.; Bonner, T. I.; Cabral, G.; Casellas, P.; Devane, W. A.; Felder, C. C.; Herkenham, M.; Mackie, K.; Martin, B. R.; Mechoulam, R.; Pertwee, R. G. *Pharmacol. Rev.* **2002**, *54*, 161–202. (g) Steffens, S.; Veillard, N. R.; Arnaud, C.; Pelli, G.; Burger, F.; Staub, C.; Zimmer, A.; Frossard, J.-L.; Mach, F. *Nature* **2005**, *434*, 782–786. (h) Lambert, D. M.; Fowler, C. J. *J. Med. Chem.* **2005**, *48*, 5059–5087.

(5) (a) Huffman, J. W. *Curr. Pharm. Des.* **2000**, *6*, 1323–1337. (b) Mahadevan, A.; Siegel, C.; Martin, B. R.; Aboot, M. E.; Beletskaya, I.; Razdan, R. K. *J. Med. Chem.* **2000**, *43*, 3778–3785. (c) Malan, T. P., Jr.; Ibrahim, M. M.; Deng, H.; Liu, Q.; Mata, H. P.; Vanderah, T.; Porreca, F.; Makriyannis, A. *Pain* **2001**, *93*, 239–245. (d) Raitio, K. H.; Salo, O. M.; Nevalainen, T.; Poso, A.; Jarvinen, T. *Curr. Med. Chem.* **2005**, *12*, 1217–1237. (e) Marriott, K. S.; Huffman, J. W. *Curr. Top. Med. Chem.* **2008**, *8*, 187–204.

(6) (a) Appendino, G.; Gibbons, S.; Giana, A.; Pagani, A.; Grassi, G.; Stavri, M.; Smith, E.; Rahman, M. M. *J. Nat. Prod.* **2008**, *71*, 1427–1430. (b) Lu, D.; Guo, J.; Duclos, I. R.; Bowman, A. L.; Makriyannis, A. *J. Med. Chem.* **2008**, *51*, 6393–6399 and references therein. (c) Radwan, M. M.; ElSoly, M.; Slade, D.; Ahmed, S. A.; Khan, I. A.; Ross, S. A. *J. Nat. Prod.* **2009**, *72*, 906–911.

(7) (a) Razdan, R. K. In *The Total Synthesis of Natural Products*; ApSimon, J., Ed.: John Wiley: New York, 1981; Vol. 4, pp 185−262. (b) Tius, M. A. In *Studies in Natural Products Chemistry*; Atta-ur-Rahaman, Ed.: Elsevier: Amsterdam, 1977; Vol. 19, pp 185. (c) Mechoulam, R.; Mccallum, N. K.; Burstein, S. *Chem. Rev.* **1976**, *76*, 75–112. (d) Handrick, G. R.; Radzan, R. K.; Uliss, D. B.; Dalzell, H. C.; Boger, E. *J. Org. Chem.* **1977**, *15*, 2563–2568. (e) Dalzell, H. C.; Uliss, D. B.; Handrick, G. R.; Razdan, R. K. *J. Org. Chem.* **1981**, *46*, 949–953. (f) Childers, W. E., Jr.; Pinnick, H. W. *J. Org. Chem.* **1984**, *49*, 5276–5277. (g) Moore, M.; Rckards, R. W.; Ronneberg, H *Aust. J. Chem.* **1984**, *37*, 2339–2348. (h) Crombie, L.; Crombie, W. M. L.; Jamieson, S. V.; Palmer, C. J. *J. Chem. Soc., Perkin Trans. 1* **1988**, 1243–1250. (i) Tchilibon, S.; Mechoulam, R. *Org. Lett.* **2000**, *2*, 3301–3303. (j) William, A. D.; Kobayashi, Y. *J. Org. Chem.* **2002**, *67*, 8771–8782. (k) Krishnamurthy, M.; Ferreira, A. M.; Moore, B. M. *Bioorg. Med. Chem.* **2003**, *13*, 3487–3490. (l) Kobayashi, Y.; Takeuchi, A.; Wang, Y.-G. *Org. Lett.* **2006**, *8*, 2699–2702. (m) Trost, B. M.; Dogra, K. *Org. Lett.* **2007**, *9*, 861–863.

(8) (a) Korte, F.; Dlugosch, E.; Claussen, U. *Liebigs Ann. Chem.* **1966**, *693*, 165–170. (b) Inoue, S.; Kosugi, C.; Lu, Z. G.; Sato, K. *Nippon Kagaku Kaishi* **1992**, 45–52. (c) Evans, D. A.; Barnes, D. M.; Johnson, J. S.; Lectka, T.; Matt, P. V.; Miller, S. J.; Murry, J. A.; Norcross, R. D.; Shaughnessy, E. A.; Kampos, K. R. *J. Am. Chem. Soc.* **1999**, *121*, 7582–7594. (d) Pearson, L. E.; Kanizaj, N.; Willis, A. C.; Michael, N. P.-R.; Sherburn, M. S. *Chem.—Eur. J.* **2010**, *16*, 8280–8284.

(9) (a) Ibata, T. In *Organic Synthesis at High Pressures*; Matsumoto, K., Achenson, R. M., Eds.; Wiley: Toronto, 1991; Chapter 9. (b) Klärner, F.-G.; Diedrich, M. K.; Wigger, A. E. In *Chemistry Under Estreme or Non-Classical Conditions*; van Eldik, R., Hubbard, C. D., Eds.; Wiley: New York, 1997; Chapter 3. (c) Jurczak, J.; Gryko, D. T. In *Chemistry Under Extreme or Non-Classical Conditions*; van Eldik, R., Hubbard, C. D., Eds.; Wiley: New York, 1997; Chapter 4. (d) Isaacs, N.S. In *High-Pressure Techniques in Chemistry and Physics*; Harwood, L. M., Moody, C. J., Eds.; Oxford: New York, 1997; Chapter 7. (e) Minuti, L.; Taticchi, A.; Costantini, L. *Recent Res. Dev. Org. Chem.* **1999**, *3*, 105–116. (f) Matsumoto, K.; Hamana, H.; Iida, H. *Helv. Chim. Acta* **2005**, *88*, 2033–2234.(g) Minuti, L. In *Eco-Friendly Processes and Procedures for the Synthesis of Fine Chemicals* (RSC Green Chemistry series); The Royal Society of Chemistry: Cambridge, U.K., 2009; Chapter 7. (h) Fringuelli, F.; Minuti, L.; Pizzo, F.; Taticchi, A. *Acta Chem. Scand.* **1993**, *47*, 255–263.

(10) Capello, C.; Fischer, U.; Hungerbühler, K. *Green Chem.* **2007**, *9*, 927–934.

(11) Kraus, G. A.; Taschner, M. J. *J. Am. Chem. Soc.* **1980**, *102*, 1974–1977.

(12) (a) Ansel, M. F.; Clements, A. H. *J. Chem. Soc. C* **1971**, 275–279. (b) Nazarov, I. N.; Titov, Yu. A.; Kuznetsova, A. I. *Doklady Akad. Nauk S.S.S.R.* **1959**, *126*, 586.

(13) (a) Kumamoto, K.; Fukada, I.; Kotsuki, H. *Angew. Chem., Int. Ed.* **2004**, *43*, 2015–2017. (b) Myers, K. E.; Kumar, K. *J. Am. Chem. Soc.* **2000**, *122*, 12055. (c) Jenner, G.; Gacem, B. *J. Phys. Org. Chem.* **2003**, *16*, 265–270.

(14) Feutrill, G. I.; Mirrington, R. N. *Tetrahedron Lett.* **1970**, 1327–1328.

(15) Song, Y.; Hwang, S.; Gong, P.; Kim, D.; Kim, S. *Org. Lett.* **2008**, *10*, 269–271.

(16) (a) Mundal, D. A.; Lutz, K. E.; Thomson, R. J. *Org. Lett.* **2009**, *11*, 465–468. (b) Kojima, T.; Yamashita, T.; Tanabe, K.; Shiragami, T.; Yasuda, M.; Shima, K. *J. Chem. Soc., Perkin Trans. 1* **1997**, 217–222. (c) Runk, C. S.; Haverty, S. M.; Klein, D. A.; McCrea, W. R.; Strobel, E. D.; Pinnick, H. W. *Tetrahedron Lett.* **1992**, *33*, 2665–2668.