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Synthesis of Tetrahydrocannabinols Based on an Indirect 1,4-Addition Strategy

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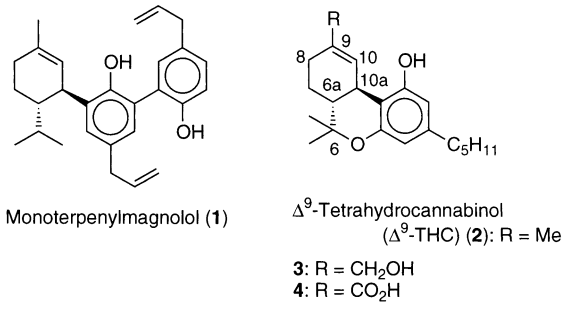
Received July 8, 2002

The synthetic procedure presented for the preparation of the title compounds requires 1,4-addition of bulky cuprates to cyclohexenones and subsequent reaction with electrophiles. However, the enolates generated by BF_3·OEt_2-assistance suffer from lack of nucleophilicity. To circumvent this problem, we developed an indirect method consisting of the following three steps: (1) iodination of the cyclohexenones at the α position; (2) BF_3·OEt_2-assisted 1,4-addition of cuprates ($Ar_2Cu(CN)Li_2$, Ar = aryl) followed by quenching the enolates with water; (3) reaction of the α-iodo-β-arylcylohexanones thus formed with EtMgBr to generate magnesium enolates. The enolates thus generated in this way showed a high reactivity toward $ClP(O)(OEt)_2$ to furnish enol phosphates. The aforementioned procedure was also applied to a synthesis of optically active Δ^9-tetrahydrocannabinol. In addition, a naphthalene analogue of the latter compound was also synthesized in a similar way.

Introduction

Figure 1 shows a class of compounds that are important in the pharmaceutical industry. Monoterpenylmagnolol (**1**),[1] extracted from the bark of *Magnolia officinalis* Rehd. et Wils., is often used in folk medicine for the treatment of bronchitis and emphysema. Δ^9-Tetrahydrocannabinol (Δ^9-THC) (**2**),[2,3] a product of the female flowering parts of *Cannabis sativa* L., is used in the treatment of patients undergoing cancer chemotherapy because of its antinauseant effect. It also possesses antiemetic, antiglaucoma, and analgesic properties. Furthermore, the metabolites of Δ^9-THC (i.e., **3** and **4**) are internal standards in analytical procedures to confirm the presence of cannabinoids in biological fluids and hence have forensic importance.[4] Recently, receptor subtypes such as CB1, CB2, and several THC analogues that bind selectively to them have been reported.[5] This opens the possibility to find the receptor-specific compound. Consequently, there is an urgent requirement for methods providing test compounds with the THC structure for further investigation. Although syntheses of compounds belonging to the THC family have been published, most of the them suffer from drawbacks such as coproduction of the more stable Δ^8-isomer, low diastereoselectivity in the preparation of the key intermediates, etc.[3,6]



Monoterpenylmagnolol (**1**)

Δ^9-Tetrahydrocannabinol (Δ^9-THC) (**2**): R = Me

3: R = CH_2OH
4: R = CO_2H

FIGURE 1. Tetrahydrocannabinol (THC) Family.

(1) Agharahimi, M. R.; LeBel, N. A. *J. Org. Chem.* **1995**, *60*, 1856−1863.

(2) (a) Razdan, R. K.*Pharmacol. Rev.* **1986**, *38*, 75−149. (b) Feigenbaum, J. J.; Richmond, S. A.; Weissman, Y.; Mechoulam, R. *Eur. J. Pharmacol.* **1989**, *169*, 159−165. (c) *Cannabinoids as Therapeutic Agents*; R. Mechoulam, Ed.; CRC Press: Boca Raton, FL, 1986. (d) Howlett, A. C.; Johnson, M. R.; Melvin, L. S.; Miline, G. M. *Mol. Pharmacol.* **1988**, *33*, 297−302.

(3) For reviews of cannabinoids synthesis, see: (a) Razdan, R. K. In *Total Synthesis of Natural Products*; ApSimon, J., Ed.; John Wiley: NewYork, 1981; Vol. 4, pp 185−262. (b) Mechoulam, R.; Mccallum, N. K.; Burstein, S. *Chem. Rev.* **1976**, *76*, 75−112.

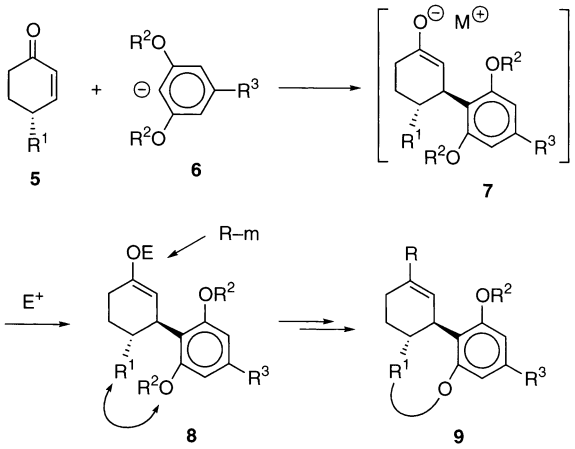
(4) (a) Agurell, S.; Halldin, M.; Lindgren, J.; Ohlsson, A.; Widman, M. *J. Pharmacol. Rev.* **1986**, *38*, 21−43. (b) Wall, M. E.; Perez- Reyes, M. *J. Clin. Pharmacol.* **1981**, *21*, 178S-189S.

(5) (a) Mahadevan, A.; Siegel, C.; Martin, B. R.; Abood, M. E.; Belestskaya, I.; Razdan, R. K. *J. Med. Chem.* **2000**, *43*, 3778−3785. (b) Drake, D. J.; Jensen, R. S.; Busch-Petersen, J.; Kawakami, J. K.; Fernandez-Garcia, M, C.; Fan, P.; Makriyannis, A.; Tius, M. A. *J. Med. Chem.* **1998**, *41*, 3596−3608. (c) Harrington, P. E.; Stergiades, I. A.; Erickson, J.; Makriyannis, A.; Tius, M. A. *J. Org. Chem.* **2000**, *65*, 6576−6582. (d) Tius, M. A.; Makriyannis, A.; Zou, X. L.; Abadji, V. *Tetrahedron* **1994**, *50*, 2671−2680.

(6) (a) Mechoulam, R.; Braun, P.; Gaoni, Y. *J. Am. Chem. Soc.* **1967**, *94*, 4552−4554. (b) Petrzilka, T.; Haefliger, W.; Sikemeier, C. *Helv. Chim. Acta* **1969**, *52*, 1102−1134. (c) Razdan, R. K.; Dalzell, H. C.; Handrick, G. R. *J. Am. Chem. Soc.* **1974**, *96*, 5860−5865. (d) Handrick, G. R.; Uliss, D. B.; Razdan, R. K. *Tetrahedron Lett.* **1979**, 681−684. (e) Crombie, L.; Crombie, W. M. L.; Jamieson, S. V.; Palmer, C. J. *J. Chem. Soc., Perkin Trans. 1* **1988**, 1243−1250. (f) Crombie, L.; Crombie, W. M. L.; Tuchinda, P. *J. Chem. Soc., Perkin Trans. 1* **1988**, 1255−1262. (g) Rickards, R. W.; Rönneberg, H. *J. Org. Chem.* **1984**, *49*, 572−573. (h) Childers, W. E., Jr.; Pinnick, H. W. *J. Org. Chem.* **1984**, *49*, 5276−5277. (i) Evans, D. A.; Barnes, D. M.; Johnson, J. S.; Lecta, T.; Von Matt, P.; Miller, S. J.; Murry, J. A.; Norcross, R. D.; Shaughnessy, E. A.; Campos, K. R. *J. Am. Chem. Soc.* **1999**, *121*, 7582−7594.

10.1021/jo020457m CCC: $22.00
Published on Web 11/19/2002

SCHEME 1. 1,4-Addition Strategy for Synthesis of Δ^9-THC Family



We envisioned, as a new method, a strategy illustrated in Scheme 1. 1,4-Addition of a protected olivetol derivative **6** to enone **5** from the less hindered β side of the enone followed by trapping of the resulting enolate **7** with an electrophile E^+ such as $ClP(O)(OEt)_2$ should provide enol **8**, which upon substitution with an appropriate anion and subsequent pyran ring cyclization would furnish the Δ^9-THC structure **9**. Herein, we describe our results of this 1,4-addition approach, which was finally completed, even though in an indirect way.[7]

Results and Discussion

Preliminary Study. Scheme 2 represents our initial investigations carried out with enone **5a**, prepared in racemic form from **19** in good overall yield by using the method of Stork (Scheme 3).[8] Although the TES ($SiEt_3$) group is usually unstable under acidic conditions, HCl-assisted hydrolysis of enol ether **21**, after the DIBAL reduction, produced **5a** in 72% yield without desilylation. 1,4-Addition of enone **5a** with the higher order cuprate $Ph_2Cu(CN)Li_2$ (**10a**) (1.5 equiv) in Et_2O at −78 °C for 2 h, followed by in situ trapping of the lithium enolate **11** with $ClP(O)(OEt)_2$ (−78 °C to room temperature), provided the enol phosphate **12a** in 63% yield.[9,10] On the other hand, attempted 1,4-addition with the bulky cuprate $Ar_2Cu(CN)Li_2$ (**10b**) (Ar is shown in the lower side of Scheme 2) at −78 to −50 °C and subsequent in situ trapping of the presumed lithium enolate **15** with $ClP(O)(OEt)_2$ did not provide enol phosphate **12b**, only starting enone **5a**. Use of $BF_3{\cdot}OEt_2$ (1 equiv) caused a dramatic change in the reactivity of the 1,4-addition.[11] Reaction in Et_2O at −78 °C for 2 h followed by aqueous workup produced the 1,4-addition product **17**[12] in 90% yield. Although the formation of boron enolate **16** was assumed, trapping of **16** as enol phosphate **12b** at −78 °C to room temperature was unsuccessful. In a control experiment, reaction of enone **5a** with the less bulky cuprate **10a** in the presence of $BF_3{\cdot}OEt_2$ afforded the 1,4-addition product **14**[12] in 80% yield after aqueous work up, but enolate trapping with $ClP(O)(OEt)_2$ did not proceed at all. Transmetalation of boron enolate **16** to lithium enolate **15** with *n*-BuLi followed by reaction with $ClP(O)(OEt)_2$ also failed, and ketone **17** was produced instead.[13,14]

These results are consistent with the observation reported by Lipshutz[15] about the unreactive nature of the boron enolate synthesized by the $BF_3{\cdot}OEt_2$-assisted 1,4-addition on sterically hindered enones. To the best of our knowledge, the difficulty of trapping the boron enolate remains unsolved.

We also attempted the TMSCl-assisted 1,4-addition of cuprate **10b** on enone **5a**, anticipating that the intermediate silyl enol ether **18** could be metalated with MeLi to afford the reactive lithium enolate **15**. However, the 1,4-addition reaction under the Nakamura conditions[16] using TMSCl and HMPA (each 2 equiv) in THF at −78 °C did not proceed, and the starting enone **5a** was recovered.

Indirect Method of the 1,4-Addition Strategy. To circumvent the intrinsic low reactivity of the boron enolate, we envisioned an indirect method disclosed in Scheme 4. The first step is iodination of enone **5** to produce α-iodo-cyclohexenone **22**. Upon 1,4-addition in the presence of $BF_3{\cdot}OEt_2$ **22** would furnish α-iodoketone **23** (step 2), which should be amenable to conversion into the reactive enolate **24** (step 3). Subsequent reaction with $ClP(O)(OEt)_2$ would afford enol phosphate **12**. In addition, reaction with other electrophiles (E^+) would furnish either enol ether **25** or ketone **26**, depending on the nature of E^+.

Iodides **22a** [R = $C(Me)_2(OTES)$], **22b** (R = Bu-*t*), and **22c** (R = H) were prepared from the corresponding enones **5a**−**c**[17] in good yields by Johnson's method[18,19] (eq 1), and submitted to the $BF_3{\cdot}OEt_2$-assisted 1,4-addition under the conditions used in Scheme 2 (Et_2O, −78 °C, 2 h). Initially, 1,4-addition of α-iodoenone **22a** [R = $C(Me)_2$-

(7) A preliminary report: William, A. D.; Kobayashi, Y. *Org. Lett.* **2001**, *3*, 2017−2020.

(8) Stork, G.; Danheiser, R. L. *J. Org. Chem.* **1973**, *38*, 1775−1776.

(9) Use of a mixed cuprate, Ph(2-Th)Cu(CN)Li_2, furnished a complex TLC pattern, which prevented isolation of the product by column chromatography, while use of $Ph_2Cu(CN)Li_2$ provided a better TLC and thus allowed easy purification.

(10) (a) Lipshutz, B. H.; Koerner, M.; Parker, D. A. *Tetrahedron Lett.* **1987**, *28*, 945−948. (b) Lipshutz, B. H.; Kozlowski, J. A.; Parker, D. A.; Nguyen, S. L.; McCarthy, K. E. *J. Organomet. Chem.* **1985**, *285*, 437−447.

(11) (a) Yamamoto, Y.; Yamamoto, S.; Yatagai, H.; Ishihara, Y.; Marumaya, K. *J. Org. Chem.* **1982**, *47*, 119−126. (b) Tius, M. A.; Kannangara, G. S. K. *J. Org. Chem.* **1990**, *55*, 5711−5714. (c) Mioskowski, C.; Manna, S.; Falck, J. R. *Tetrahedron Lett.* **1983**, *24*, 5521−5524. (d) Ghirbi, A.; Alexakis, A.; Normant, J. F. *Tetrahedron Lett.* **1984**, *25*, 3075−3086.

(12) ^{1}H NMR spectra. **14**: ^{1}H NMR δ 0.58 (q, J = 8 Hz, 6 H), 0.94 (t, J = 8 Hz, 9 H), 1.12 (s, 3 H), 1.18 (s, 3 H), 1.81−2.62 (m, 6 H), 2.69 (dd, J = 15, 6 Hz, 1 H), 3.35 (q, J = 7 Hz, 1 H), 7.13−7.32 (m, 5 H). **17**: ^{1}H NMR δ 0.55 (q, J = 8 Hz, 6 H), 0.85−1.00 (m, 12 H), 1.08 (s, 3 H), 1.16 (s, 3 H), 1.25−1.40 (m, 6 H), 1.50−1.65 (m, 2 H), 1.75−1.95 (m, 1 H), 2.25−2.75 (m, 6 H), 3.47 (s, 6 H), 3.93 (q, J = 7 Hz, 1 H), 5.10−5.20 (m, 4 H), 6.60 (s, 2 H).

(13) (a) Batt, D. G.; Takamura, N.; Ganem, B. *J. Am. Chem. Soc.* **1984**, *106*, 3353−3354. (b) McMurry, J. E.; Scott, W. J. *Tetrahedron Lett.* **1983**, *24*, 979−982.

(14) Enolate trapping study as a triflate with other electrophiles such as Tf_2NPh, Tf_2O was unsuccessful.

(15) Lipshutz, B. H.; Parker, D. A.; Kozlowski, J. A.; Nguyen, S. L. *Tetrahedron Lett.* **1984**, *25*, 5959−5962.

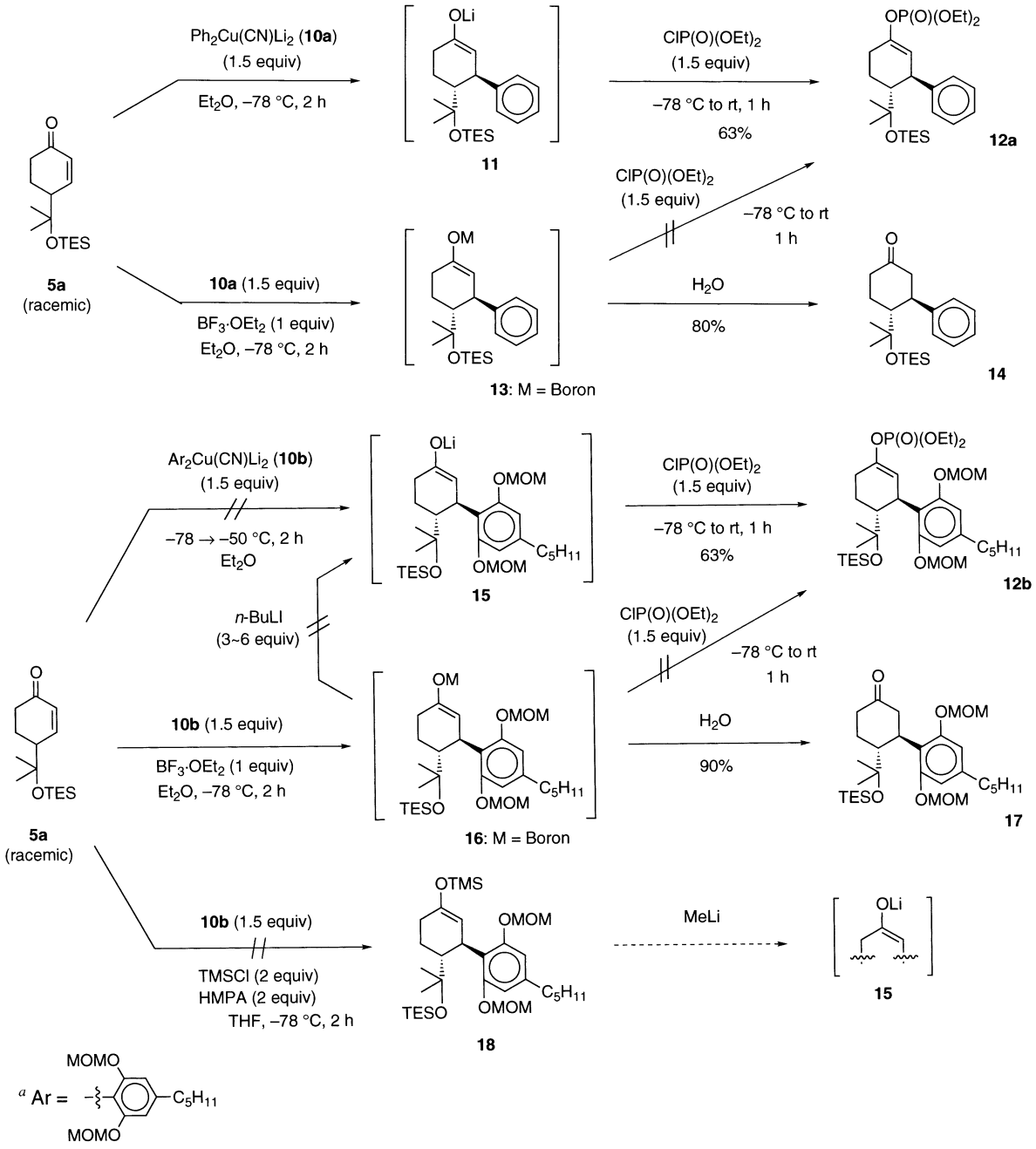
(16) Nakamura, E.; Matsuzawa, S.; Horiguchi, Y.; Kuwajima, I. *Tetrahedron Lett.* **1986**, *27*, 4029−4032.

(17) Enone **5b** (R = Bu-*t*) was prepared according to Garbisch with comparable yields: Garbisch, E, W., Jr. *J. Org. Chem.* **1965**, *30*, 2109−2120.

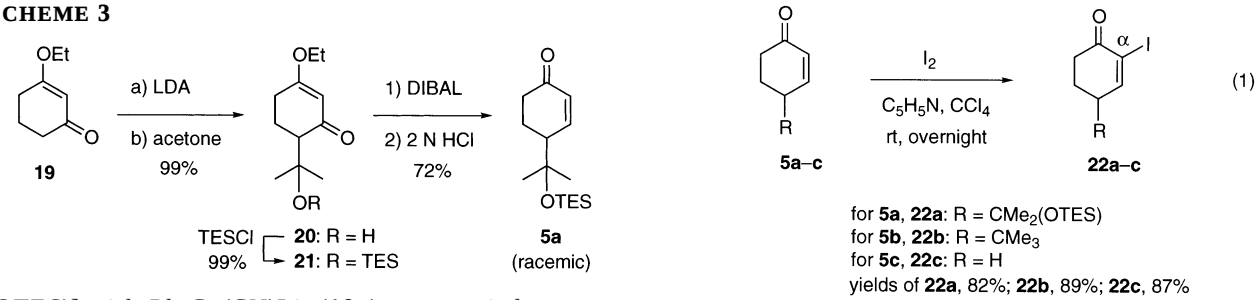
(18) Johnson, C. R.; Adams, J. P.; Braun, M. P.; Senanayake, C. B. W.; Wovkulich, P. M.; Uskokovi'c, M. R.*Tetrahedron Lett.* **1992**, *33*, 917−918.

(19) Yield of enone **22c**[18] (R = H) was improved to 87% yield.

SCHEME 2[a]



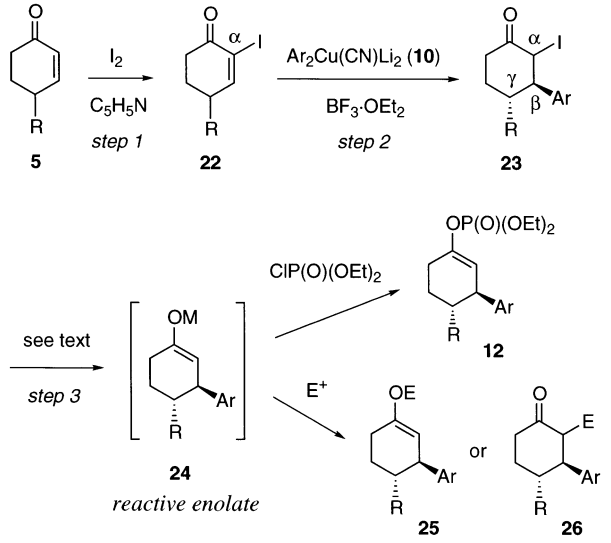
SCHEME 3



(OTES)] with $Ph_2Cu(CN)Li_2$ (**10a**) was carried out as a control experiment to afford α-iodoketone **23a** in 65% yield (Table 1, entry 1). Under the same reaction conditions, the more bulky reagent **10b** furnished **23b** in 72% yield (entry 2). The yields were comparable in both cases, and hence demonstrate the high performance of the present procedure. In both cases, no reaction at the α site of the enones was observed by ^1H NMR spectroscopy.[20]

Reaction of **22a** with the olivetol-derived cuprates **10c** and **10d** also produced ketones **23c** and **23d**, respectively,

SCHEME 4. Our Approach to Enol Phosphates 12[a]



[a] For specific compounds: **5a**−**c** and iodoenones **22a**−**c**, see eq 1; cuprates **10a**−**e**, ketones **23a**−**h**, and phosphates **12a**−**h**, see Table 1.

in reasonable yields[21] (entries 3 and 4). Furthermore, the naphthalene cuprate **10e** afforded the addition product **23e** in 74% yield without any difficulty (entry 5). As is evident from these results, the 1,4-addition has no restriction on the size of the cuprate [$Ar_2Cu(CN)Li_2$].

1,4-Addition using other enones **22b** (R = *t*-Bu) and **22c** (R = H) was also successful, as is seen in entries 6−8. These results clearly show that the size of the substituent at the γ position of the enones has little influence on the reaction.

The determination of the relative stereochemistry at the β and γ positions of the 1,4-addition products **23a**−**h** by ^{1}H NMR spectroscopy was ambiguous as a result of varying coupling constants (4.5−7.5 Hz) between the protons at these positions.[22] However, the stereochemistry of **23c** was determined to be trans by synthesis of Δ^9-THC (**2**) (vide infra).[23] This assignment is consistent with the steric approach control of cuprate **10c** to α-iodoenone **22a**. We assume that the same (trans) configuration is valid for the products of the other entries of Table 1.

Generation of Enolates from α-Iodoketones. The several protocols reported for similar types of the conversion were applied preliminary to α-iodoketone **23b** with the MOM protecting group on the aromatic ring. The conditions of Stork,[24] Borowitz,[25] and Pande[26] were not suitable for generating enolate **24b**, since **23b** was recovered unchanged after the reactions (Table 2, entries 1−3).

Attempted reactions using $Et_3B/Ph_3SnH/C_6H_6$, Et_3B/Et_2O or C_6H_6, and *n*-BuLi/Et_2O according to Utimoto[27] also failed to provide enolate **24b** (entries 4−6). Fortunately, EtMgBr (1.5 equiv) in THF at 0 °C[27b] furnished the magnesium enolate **24b** (M = MgBr), which was trapped with $ClP(O)(OEt)_2$ (2.5 equiv) at 0 °C for 2 h to produce the desired enol phosphate **12b** in 71% yield (entry 7). In this case, the reaction in THF was cleaner than that in Et_2O.[27b]

The conditions found suitable for conversion of **23b** to enol phosphate **12b** were applied successfully to other α-iodoketones **23a** and **23c**−**h** to yield enol phosphates **12a** and **12c**−**h** in good yields as presented in Table 1 (entries 1, 3−8). During these investigation, no difference in reactivity was observed between olivetol moieties (entries 2−4, 6, and 7) and the naphthalene moiety (entries 5 and 8).

Reactivity of the Magnesium Enolate toward Aldol Reaction. Although Utimoto reported aldol reactions of the magnesium enolate derived from simple α-iodoketones with simple aldehydes,[27b] aldol reactions of congested magnesium enolates were briefly studied, since the interference of the bulky aryl groups at the β position was not predictable. Such information on the reactivity would be useful in organic synthesis.

Magnesium enolate **24b**, generated from iodoketone **23b** and EtMgBr in THF, was submitted to aldol reaction with aldehyde **27** at 0 °C (Scheme 5). The reaction proceeded efficiently to afford aldol **28**[28] in 79% yield. Likewise, formaldehyde afforded aldol **29**[28] in 64% yield, which was a 2:1 mixture of the diastereoisomers by ^{1}H NMR spectroscopy. These results clearly show that the steric influence of the bulky aryl group at the β position on the reactivity at the α position is negligibly small, and hence other aldehydes would be equally compatible with the aldol reaction of the magnesium enolates **24** (M = MgBr). In addition, aldol **29** was converted into the corresponding mesylate, which was exposed to Al_2O_3 in CH_2Cl_2[29] to produce the exocyclic enone **30**[30] in good yield.

Conversion of Enol Phosphates into Corresponding Methyl- and Hydroxymethyl Compounds. The next step toward the synthesis of Δ^9-THC structure shown in Scheme 1 is conversion of enol phosphate **8** (E = $P(O)(OEt)_2$) (= **12** of Scheme 4) into the corresponding

(20) Cf.: (a) Negishi, E.; Owczarczyk, Z. R.; Swanson, D. R. *Tetrahedron Lett.* **1991**, *32*, 4453−4456. (b) Johnson, C. R.; Adams, J. P.; Braun, M. P.; Senanayake, C. B. W. *Tetrahedron Lett.* **1992**, *33*, 919−922.

(21) In entry 4, yield was calculated after conversion of semipurified α-iodoketone **23d** to its enol phosphate **12d** (vide infra) because of the similar R_f value for **23d** and the SEM ether of olivetol derived from the copper reagent after workup.

(22) In addition, the stereochemistry at the α position was not determined because of the next step of the enol formation reaction.

(23) The characteristic signals for Δ^9-THC (**2**) and its cis isomer in the ^{1}H NMR spectra appear at 3.14 and 3.59 ppm, respectively, whereas that for the *trans*-Δ^8-isomer appears at 3.25 ppm: Taylor, E. C.; Lenard, K.; Shvo, Y. *J. Am. Chem. Soc.* **1966**, *88*, 367−368.

(24) Stork, G.; Isobe, M. *J. Am. Chem. Soc.* **1975**, *97*, 4745−4746.

(25) Borowitz, I. J.; Anschel, M.; Firstenberg, S. *J. Org. Chem.* **1967**, *32*, 1723−1729. (b) Borowitz, I. J.; Casper, E. W. R.; Crouch, R. K.; Yee, K. C. *J. Org. Chem.* **1972**, *37*, 3873−3878.

(26) (a) Joshi, G. C.; Pande, L. M. *Synthesis* **1975**, 450−452. (b) Hashimoto, S.; Itoh, A.; Kitagawa, Y.; Yamamoto, H.; Nozaki, H. *J. Am. Chem. Soc.* **1977**, *99*, 4192−4194.

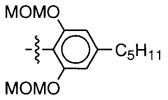
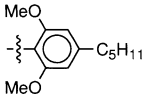
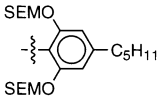
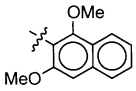
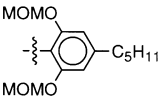
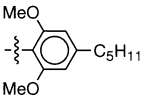
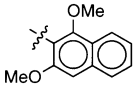
(27) (a) Nozaki, K.; Oshima, K.; Utimoto, K. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 403−409. (b) Aoki, Y.; Oshima, K.; Utimoto, K. *Chem. Lett.* **1995**, 463−464.

(28) Because of the complex nature of the ^{1}H NMR signals, the stereochemistry of the α carbon center was not determined.

(29) (a) Posner, G. H.; Gurria, G. M.; Babiak, K. A. *J. Org. Chem.* **1977**, *42*, 3173−3180. (b) Yamada, K.; Arai, T.; Sasai, H.; Shibasaki, M. *J. Org. Chem.* **1998**, *63*, 3666−3672. (c) Kobayashi, Y.; Murugesh, M. G.; Nakano, M. *Tetrahedron Lett.* **2001**, *42*, 1703−1707.

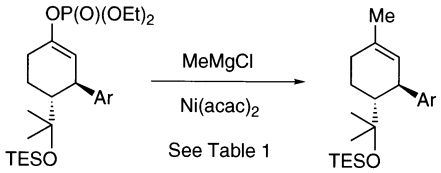
(30) Although further stirring at room temperature for longer time after completion of the mesylation in one flask produced enone **30**, the reaction was not completed and produced byproduct(s).

TABLE 1. Synthesis of 1,4-Addition Products 23a–h, Enol Phosphates 12a–h, and Methylation Products 31a–e

	enone		cuprate		22 → 23		23 → 12		12 → 31	
entry	**22**	R	**10**	Ar	**23**	yield, %	**12**	yield, %	**31**	yield, %
1	**22a**	$C(Me)_2(OTES)$	**10a**		**23a**	65	**12a**	63	**31a**	94
2	**22a**	$C(Me)_2(OTES)$	**10b**		**23b**	72	**12b**	71[a]	**31b**	92
3	**22a**	$C(Me)_2(OTES)$	**10c**		**23c**	67	**12c**	70	**31c**	90
4	**22a**	$C(Me)_2(OTES)$	**10d**		**23d**	–[b]	**12d**	53[b]	**31d**	93
5	**22a**	$C(Me)_2(OTES)$	**10e**		**23e**	74	**12e**	60	**31e**	99
6	**22b**	Bu-*t*	**10b**		**23f**	67	**12f**	63	–	–
7	**22c**	H	**10c**		**23g**	60	**12g**	58	–	–
8	**22c**	H	**10e**		**23h**	68	**12h**	62	–	–

[a] Result of Table 2, entry 7. [b] The yield was obtained for **12d** (two-step yield).

methyl derivative.[31] As shown in eq 2, this conversion,



12a–e **31a–e** (2)

examined first with **12b**, was accomplished by using MeMgCl in the presence of $Ni(acac)_2$ catalyst in THF at room temperature overnight to produce **31b** in 92% yield, as is presented in entry 2 of Table 1. In a similar manner, olivetol-derived phosphates **12c**,**d**, naphthalene phosphate **12e**, and model phosphate **12a** were all successfully converted into the methyl products **31c**–**e** and **31a** in good yields (entries 3–5 and 1 of Table 1).

The above procedure was applied to $ClMgCH_2SiMe_2$-(OPr-*i*) (**32**) which has been shown to be a synthetic equivalent of the CH_2OH anion.[32] The reaction with **12b** and **12c** at room temp. overnight proceeded smoothly to furnish **33b** and **33c** in good yields (Scheme 6), and subsequent oxidation with 35% H_2O_2 in the presence of KF and $NaHCO_3$ in THF and MeOH at 50 °C provided **34b** and **34c** in 58% and 52% yields, respectively. The products **34b**,**c** would be converted into Δ^9-THC metabolites such as **3** and **4** (Figure 1).[33]

Synthesis of Δ^9-THC and Its Naphthalene Analogue in Racemic Form. The next step toward the synthesis of Δ^9-THC was the removal of the protective groups on the aromatic ring and subsequent construction of the pyran ring. Among three candidates **31b**–**d**, compound **31b** with the MOM protection on its aromatic part was initially chosen with the expectation that the acidic conditions would facilitate deprotection of both the MOM and TES groups and simultaneous cyclization to provide the pyran in one flask. However, no reagent was found to provide the desired Δ^9-THC (**2**) (Table 3): the regioisomeric product, Δ^8-THC (**35**), was obtained with catecholborane in CH_2Cl_2[34] and P_2I_4 in CH_2Cl_2[35] (entries 1,2), while NaI in acetone with a trace amount of HCl,[36] PPTS in acetone[37] furnished alcohol **36** as a sole product,

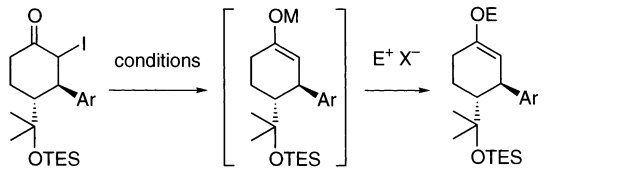
(31) (a) Hayashi, T.; Fujiwa, T.; Okamoto, Y.; Katsuro, Y.; Kumada, M. *Synthesis* **1981**, 1001–1003. (b) Sahlberg, C.; Quader, A.; Claesson, A. *Tetrahedron Lett.* **1983**, *24*, 5137–5138.

(32) (a) Tamao, K.; Ishida, N. *Tetrahedron Lett.* **1984**, *25*, 4245–4248. (b) Tamao, K.; Maeda, K. *Tetrahedron Lett.* **1986**, *27*, 65–68.

(33) This conversion is now under investigation.

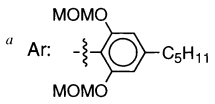
(34) Boeckman, R. K., Jr.; Potenza, J. C. *Tetrahedron Lett.* **1985**, *26*, 1411–1414.

TABLE 2. Attempts To Synthesize Enol Derivatives through Reactive Enolates[a]



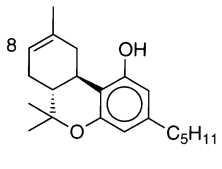
23b **24b** **25b**, E: TMS **12b**, E: P(O)(OEt)$_2$

entry	reagent/conditions	$E^+ X^-$	results[b]
1	$MeOPPh_2$ /$CHCl_3$, rt–reflux, 2 h	–	NR
2	$P(OEt)_3$ /EtOH or $CHCl_3$, rt–reflux, 6 h	–	NR
3	Zn /THF, rt, 8 h	TMSCl	NR
4	BEt_3, Ph_3SnH /C_6H_6, 0 °C, 2 h	$ClP(O)(OEt)_2$	mixture
5	BEt_3 /Et_2O or C_6H_6, rt, 2 h	$ClP(O)(OEt)_2$	NR
6	*n*-BuLi /Et_2O, 0 °C, 0.5 h	$ClP(O)(OEt)_2$	mixture
7[c]	EtMgBr /THF, 0 °C, 2 h	$ClP(O)(OEt)_2$	**12b**, 71%

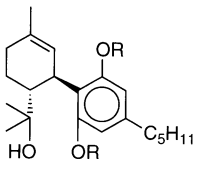
[a] Ar: 

[b] NR: no reaction. [c] This result is again presented in entry 2 of Table 1.

in which only the TES group was removed (entries 3 and 4). The use of $LiBF_4$ in aqueous MeCN[38] resulted in formation of complex mixture (entry 5).



35

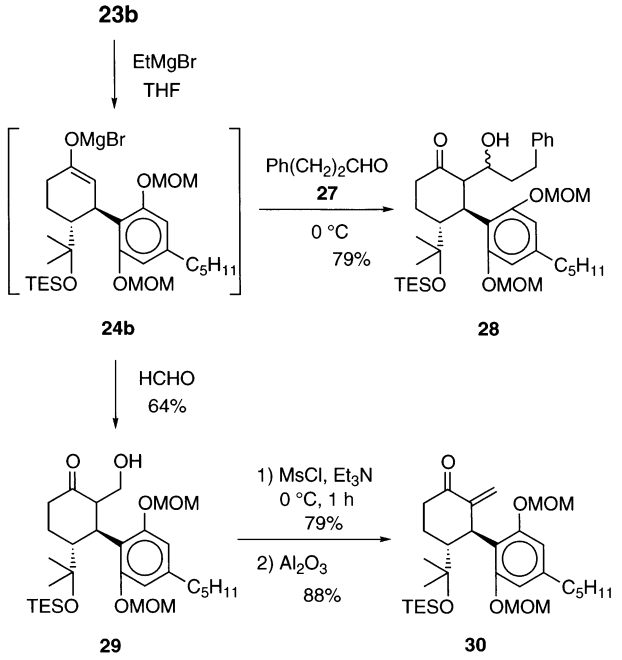


36, R = MOM
37, R = SEM

Next examined was the SEM ether **31d**, which on treatment with TBAF under several conditions[39] led to deprotection of the TES group giving **37** or to decomposition (Table 4).

Fortunately, deprotection of the *O*-methylated derivative **31c** was accomplished successfully. On exposure of **31c** to NaSEt in DMF at 140 °C according to Feutrill,[40] monodemethylation and desilylation took place simultaneously to furnish diol **38** in 70% yield (Scheme 7). Attempted one-step deprotection of all of the protecting groups on **31c** at higher temperature (>140 °C) was unsuccessful. Cyclization of diol **38** by using the protocol

SCHEME 5. Aldol Reactions of the Magnesium Enolate 24b



SCHEME 6

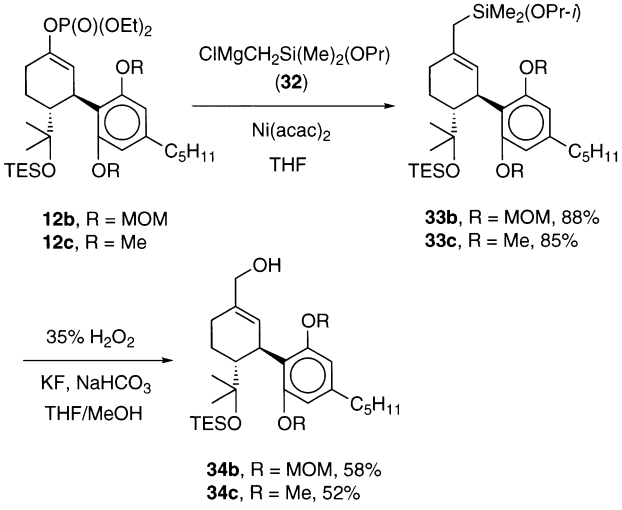


TABLE 3. Attempted Deprotection of MOM Groups on 31b

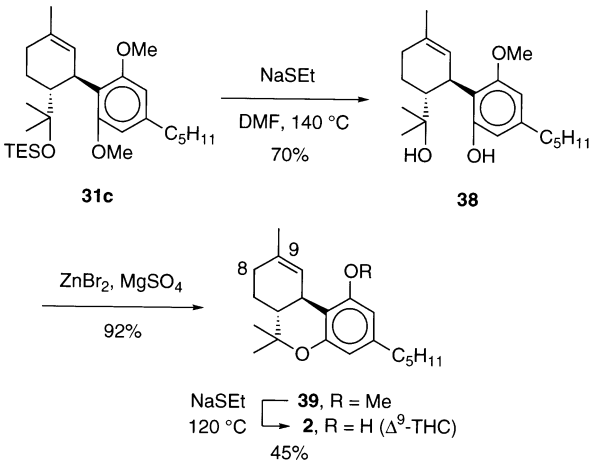
entry	conditions	results
1	catecholborane/CH_2Cl_2, 0 °C, 1 h	**35**
2	P_2I_4/CH_2Cl_2, 0 °C, 2 h	**35**
3	NaI/acetone/trace HCl, rt, 0.5 h	**36**
4	PPTS/acetone, rt−reflux, 12 h	**36**
5	$LiBF_4$/MeCN/H_2O, 60−70 °C, 2 h	complex mixture

(35) Saimoto, H.; Kusano, Y.; Hiyama, T. *Tetrahedron Lett.* **1986**, *27*, 1607−1610.
(36) Williams, D. R.; Barner, B. A.; Nishitani, K.; Phillips, J. G. *J. Am. Chem. Soc.* **1982**, *104*, 4708−4710.
(37) Monti, H.; Leandri. G.; Klos-Ringquet, M.; Corriol, C. *Synth. Commun.* **1983**, *13*, 1021−1026.
(38) Ireland, R. E.; Varney, M. D. *J. Org. Chem.* **1986**, *51*, 635−648.
(39) Lipshtuz, B. H.; Miller, T. A. *Tetrahedron Lett.* **1989**, *30*, 7149−7152.
(40) Feutrill, G. I.; Marrington, R. N. *Tetrahedron Lett.* **1970**, 1327−1328.

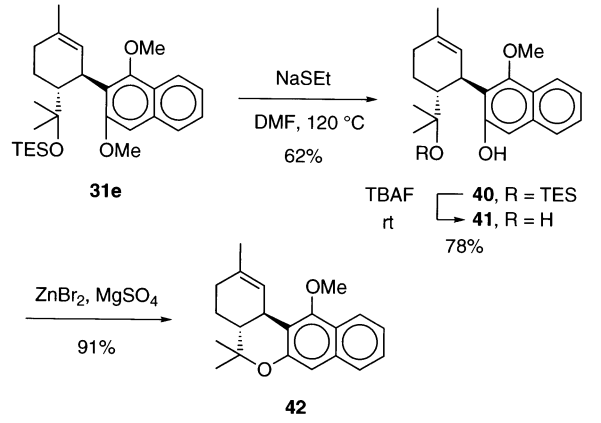
TABLE 4. Attempted Deprotection of SEM Groups on 31d

entry	conditions	results
1	TBAF/THF, 80 °C, 2 h	**37**
2	TBAF/HMPA/THF, 60−80 °C, 2 h	**37**
3	TBAF/HMPA/4Å MS, >100 °C	complex mixture

SCHEME 7. Racemic Synthesis of Δ^9-THC



SCHEME 8



of Evans[6i] furnished the cyclized product **39** in 92% yield. Finally, the remaining methyl group on **39** was removed with NaSEt at 120 °C in DMF[6h] to provide Δ^9-THC (**2**) in 45% yield. The ^{1}H NMR (300 MHz) spectrum of synthetic **2** thus synthesized was identical with that reported,[6i] thus confirming the trans stereochemistry and thence the steric approach control of cuprate **10c** to enone **22a** (Scheme 4). In addition, the spectrum clearly shows no contamination of Δ^8-isomer **35** in product **2**.[23]

In order to prove the efficiency of our 1,4-addition strategy for building up the THC structure, naphthalene analogue **42** was synthesized starting from the racemic key intermediate **31e** (Scheme 8). Although the temperature used for **31c** (i.e., 140 °C) furnished a complex mixture, lower temperature (120 °C) allowed clean deprotection, giving **40**[41] in 62% yield. Deprotection of the TES group of **40** with TBAF afforded diol **41** in 78% yield, which was cyclized with $ZnBr_2$ and $MgSO_4$ to furnish the first maphthalene analogue **42** of Δ^9-THC in 91% yield. The ^{1}H NMR spectrum indicated absence of the Δ^8-isomer.

Synthesis of Δ^9-THC in Optically Active Form. Having performed the synthesis of racemic Δ^9-THC, our attention was focused on synthesis of optically active Δ^9-THC ((−)-**2**), in which the (*R*)-isomer of **5a** was required as one of the key intermediates. This isomer was synthesized from (+)-*β*-pinene (**43**) as depicted in Scheme 9. According to reported procedures, ozonolysis[42] of **43** ($[\alpha]^{20}_D$ +21 (neat); from Aldrich) followed by the cyclobutane ring opening[43] of **44** with $Zn(OAc)_2$ and BF_3·OEt_2 in Ac_2O furnished enol acetate **45** in 72% yield ($[\alpha]^{26}_D$ +45° (*c* 0.47, EtOH); lit.[44a] $[\alpha]^{29.5}_D$ −48.3° (*c* 0.0325, EtOH) for the enantiomer). Conversion of **45** to enone **46** was carried out in 85% yield with allyl ethyl carbonate in the presence of $Pd(OAc)_2$, DPPE, and Bu_3SnOMe.[45] Removal of the acetyl (Ac) group from **46** was achieved by reduction with DIBAL-H to furnish diol **47** in 94% yield. Subsequent oxidation with PCC afforded enone **48** in 76% yield ($[\alpha]^{29}_D$ +72° (*c* 0.44, MeOH)). Finally, enone **48** was converted to the TES ether (+)-**5a** in 85% ($[\alpha]^{24}_D$ +67°(*c* 0.49, MeOH)).

The sequence we have established for the synthesis of racemic Δ^9-THC was traced with optically active enone (+)-**5a** to complete the synthesis of optically active Δ^9-THC ((−)-**2**) through the key intermediates (−)-**22a** ($[\alpha]^{28}_D$ −5 (c 0.96, MeOH)), (−)-**12c** ($[\alpha]^{30}_D$ −43° (*c* 0.53, $CHCl_3$)), and (−)-**31c** ($[\alpha]^{28}_D$ −84° (*c* 0.49, $CHCl_3$)). The optical rotation of (−)-**2** thus synthesized was in good agreement with that reported ($[\alpha]^{30}_D$ −145° (*c* 0.11, $CHCl_3$), lit.[6b] ($[\alpha]^{28}_D$ −150° (*c* 1.0, $CHCl_3$)).

Conclusion

We established an indirect method to generate reactive magnesium enolates after the BF_3·OEt_2-assisted 1,4-addition of cuprates [$R_2Cu(CN)Li_2$] to enones. The method is especially convenient when less reactive cuprates are used. By means of this method, optically pure Δ^9-THC (**2**) and a naphthalene analogue were synthesized.

Experimental Section

General Methods. Infrared (IR) spectra are reported in wavenumbers (cm^{-1}). The ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were measured in $CDCl_3$ using $SiMe_4$ (δ = 0 ppm) and the center line of $CDCl_3$ triplet (δ = 77.1 ppm) as internal standards, respectively. Signal patterns are indicated as br s, broad singlet; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Coupling constants *(J)* are given in hertz (Hz). The coupling constants between ^{13}C and ^{31}P of the enol phosphates are given in the ^{13}C NMR spectral data. Some of the signals in the ^{13}C NMR spectra appearing as broad singlets

(41) Although no evidence about the site of the demethylation was obtained from the ^{1}H NMR spectrum of the product, we are speculating that the less hindered methyl group underwent the demethylation to produce **40**.

(42) Grimshaw, J.; Grimshaw, J. T.; Juneja, H. R. *J. Chem. Soc., Perkin Trans 1* **1972**, 50−52.

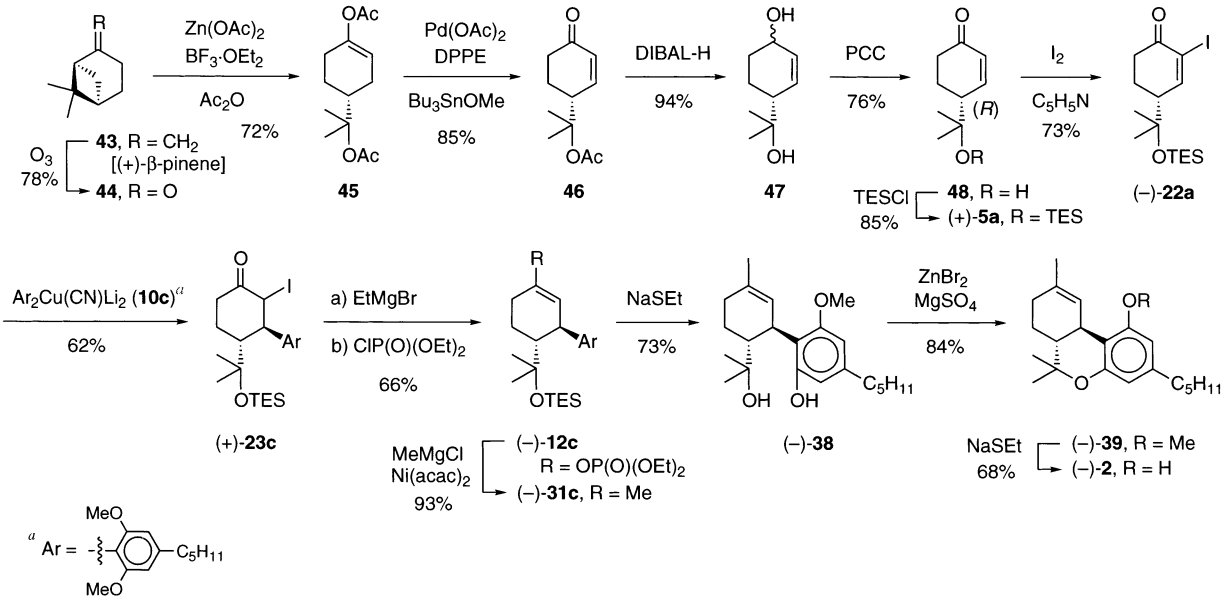
(43) (a) Kato, M.; Watanabe, M.; Vogler, B.; Tooyama, Y.; Yoshikoshi, A. *J. Chem. Soc., Chem. Commun.* **1990**, 1706−1707. (b) Kato, M.; Kamat, V. P.; Tooyama, Y.; Yoshikoshi, A. *J. Org. Chem.* **1989**, *54*, 1536−1538.

(44) (a) Siegel, C.; Gorden, P. M.; Uliss, D. B.; Handrick, G. R.; Dalzell, H. C.; Razdan, R. K. *J. Org. Chem.* **1991**, *56*, 6865−6872. (b) Gordon, P. M.; Siegel, C.; Razdan, R. K. *J. Chem. Soc., Chem. Commun.* **1991**, 692−694.

(45) Tsuji, J.; Minami, I.; Shimizu, I. *Tetrahedron Lett.* **1983**, *24*, 5639−5640.

(46) Purchased from ICN (Alumina N-Super I).

SCHEME 9. Synthesis of Optically Active Δ⁹-THC



with low intensity, probably owing to the restriction of free rotation of the aromatic ring are represented as br s. Routinely, an organic extract was dried over $MgSO_4$ and concentrated by using a rotary evaporator to leave a residual oil, which was purified by chromatography on silica gel.

6-[(1-Hydroxy-1-methyl)ethyl]-3-ethoxy-2-cyclohexen-1-one (20). To an ice-cold solution of (*i*-Pr)$_2$NH (7.2 mL, 51.4 mmol) in THF (60 mL) was added slowly a solution of *n*-BuLi (18.9 mL, 2.26 M in hexane, 42.7 mmol). The solution was stirred for 15 min and cooled to −78 °C. Enone **19** (4.15 mL, 28.5 mmol) was added to the solution. After 2 h of stirring at −78 °C, acetone (4.20 mL, 57.1 mmol) was added. The solution was stirred at −78 °C for additional 30 min and poured into an ice-cold mixture of saturated NH_4Cl and Et_2O (1:1). The organic layer was separated, and the aqueous layer was extracted with Et_2O twice. The combined organic extracts were dried and concentrated to afford an oil, which was purified by chromatography (hexane/EtOAc) to furnish **20** (5.58 g, 99% yield): IR(neat) 3426, 1605 cm^{-1}; ^{1}H NMR δ 1.21 (s, 3 H), 1.22 (s, 3 H), 1.38 (t, J = 7 Hz, 3 H), 1.71 (dq, J = 13, 5 Hz, 1 H), 1.98−2.16 (m, 1 H), 2.33 (dd, J = 13, 4.5 Hz, 1 H), 2.42 (dq, J = 17, 2.5 Hz, 1 H), 2.53 (dddd, J = 17, 13, 4.5, 1.5 Hz, 1 H), 3.84−4.00 (m, 2 H), 5.35 (d, J = 1.5 Hz, 1 H), 5.68 (s, 1 H); ^{13}C NMR δ 14.2, 24.3, 24.5, 28.6, 29.3, 54.2, 64.6, 72.6, 103.3, 178.2, 203.2. Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 66.22; H, 9.12.

6-[(1-Methyl-1-triethylsilyloxy)ethyl]-3-ethoxy-2-cyclohexen-1-one (21). A mixture of alcohol **20** (5.00 g, 25.2 mmol), TESCl (5.58 mL, 32.8 mmol), and imidazole (2.74 g, 40.2 mmol) in DMF (50 mL) was stirred overnight at ambient temperature and poured into a 1:1 mixture of saturated $NaHCO_3$ and hexane at 0 °C with vigorous stirring. The organic layer was separated, and the aqueous layer was extracted with hexane twice. The combined organic extracts were dried and concentrated to afford an oily residue, which was purified by chromatography (hexane/EtOAc) to furnish **21** (7.80 g, 99% yield): IR (neat) 1654, 1612 cm^{-1}; ^{1}H NMR δ 0.46−0.56 (m, 6 H), 0.88 (t, J = 8 Hz, 9 H), 1.23 (s, 3 H), 1.30 (t, J = 7 Hz, 3 H), 1.43 (s, 3 H), 1.90−2.30 (m, 4 H), 2.50−2.64 (m, 1 H), 3.82 (q, J = 7 Hz, 2 H), 5.24 (s, 1 H); ^{13}C NMR δ 6.9, 7.2, 14.3, 22.9, 27.2, 28.4, 31.0, 55.9, 64.0, 75.1, 103.9, 177.0, 200.1. Anal. Calcd for $C_{17}H_{32}O_3Si$: C, 65.33; H, 10.32. Found: C, 65.21; H, 10.38.

4-[(1-Methyl-1-triethylsilyloxy)ethyl]-2-cyclohexen-1-one (5a). To a solution of ketone **21** (8.00 g, 25.6 mmol) in THF (50 mL) at −78 °C was added DIBAL (51.2 mL, 1.0 M in hexane, 51.2 mmol). After 1 h of stirring at −78 °C, the reaction was quenched by slow addition of H_2O (18.4 mL, 1.02 mmol) dissolved in THF (40 mL). The mixture was stirred at ambient temperature for 1 h. NaF (8.60 g) was added to the mixture, and stirring was continued for additional 1 h. The reaction mixture was filtered through a pad of Celite with EtOAc, and the filtrate was evaporated under reduced pressure to afford the corresponding alcohol (8.00 g) as an oil, which was taken as such for the next the step.

To an ice-cold solution of the above crude alcohol (8.00 g) in Et_2O (150 mL) was added 2 N HCl (150 mL). After 45 min of vigorous stirring at ambient temperature, the mixture was diluted with H_2O, and the organic layer was separated. The aqueous layer was extracted with Et_2O. The combined organic layers were washed with saturated $NaHCO_3$ and brine, dried, and concentrated to afford an oily residue, which was purified by chromatography (hexane/EtOAc) to furnish **5a** (4.92 g, 72% yield from **21**): IR (neat) 1684 cm^{-1}; ^{1}H NMR δ 0.52−0.62 (m, 6 H), 0.92 (t, J = 8 Hz, 9 H), 1.15 (s, 3 H), 1.26 (s, 3 H), 1.60−1.76 (m, 1 H), 2.00−2.12 (m, 1 H), 2.31 (ddd, J = 16, 14, 5 Hz, 1 H), 2 41 (dq, J = 11, 2 Hz, 1 H), 2.48 (dt, J = 16, 3 Hz, 1 H), 6.01 (ddd, J = 10, 3, 1 Hz, 1 H), 7.12 (dt, J = 10, 2 Hz, 1 H); ^{13}C NMR δ 6.9, 7.2, 24.8, 26.6, 28.3, 37.6, 49.2, 74.7, 129.7, 152.7, 199.8. Anal. Calcd for $C_{15}H_{28}O_2Si$: C, 67.11; H, 10.51. Found: C, 66.80; H, 10.67.

2-Iodo-4-[(1-methyl-1-triethylsilyloxy)ethyl]-2-cyclohexen-1-one (22a). To an ice-cold solution of enone **5a** (1.00 g, 3.72 mmol) in CCl_4 (10 mL) and pyridine (10 mL) was added a solution of I_2 (2.84 g, 11.2 mmol) dissolved in CCl_4 and pyridine (1:1, 20 mL). After stirring overnight at ambient temperature, the mixture was diluted with Et_2O and H_2O. The organic layer was separated, and the aqueous layer was extracted with Et_2O twice. The combined organic layers were washed with saturated $Na_2S_2O_3$ and H_2O, dried, and evaporated to afford an oily residue, which was purified by chromatography (hexane/EtOAc) to furnish **22a** (1.20 g, 82% yield): IR (neat) 1690, 1585 cm^{-1}; ^{1}H NMR δ 0.57−0.67 (m, 6 H), 0.97 (t, J = 8 Hz, 9 H), 1.10 (s, 3 H), 1.32 (s, 3 H), 1.72−1.88 (m, 1 H), 2.09−2.20 (m, 1 H), 2.41−2.60 (m, 2 H), 2.81 (dt, J = 17, 4 Hz, 1 H), 7.92 (dd, J = 2, 1.8 Hz, 1 H); ^{13}C NMR δ 6.9, 7.3, 24.9, 26.8, 28.4, 36.3, 53.6, 74.5, 103.9, 161.7, 192.3. Anal. Calcd for $C_{15}H_{27}IO_2Si$: C, 45.68; H, 6.90. Found: C, 45.66; H, 6.86.

2-Iodo-4-[(1,1-dimethyl)ethyl]-2-cyclohexen-1-one (22b). To an ice-cold solution of 4-[(1,1-dimethyl)ethyl]-2-cyclohexen-1-one (**5b**)[17] (2.00 g, 13.1 mmol) in CCl_4 (25 mL) and pyridine

(25 mL) was added a solution of I_2 (10.0 g, 39.4 mmol) dissolved in CCl_4 (25 mL) and pyridine (25 mL). After the mixture was stirred overnight at ambient temperature, Et_2O and H_2O were added to the reaction mixture. The organic layer was separated, and the aqueous layer was extracted with Et_2O twice. The combined organic layers were washed sequentially with 1 N HCl, saturated $Na_2S_2O_3$, and H_2O, dried, and concentrated to afford an oily residue, which was purified by chromatography (hexane/EtOAc) to furnish **22b** (3.25 g, 89% yield): IR (neat) 1671, 1578 cm^{-1}; ^1H NMR δ 0.99 (s, 9 H), 1.73−1.89 (m, 1 H), 2.09−2.22 (m, 1 H), 2.31−2.55 (m, 2 H), 2.81 (dt, J = 16, 4 Hz, 1 H), 7.77 (t, J = 2 Hz, 1 H); ^{13}C NMR δ 24.1, 27.1, 32.8, 36.2, 51.0, 104.0, 161.3, 191.5. Anal. Calcd for $C_{10}H_{15}IO$: C, 43.18; H, 5.44. Found: C, 43.03; H, 5.69.

2-Iodo-2-cyclohexen-1-one (22c). The title compound was prepared by the procedure of Johnson[18] in better yield. Briefly, a mixture of enone **5c** (500 mg, 5.2 mmol) and I_2 (3.96 g, 15.60 mmol) in CCl_4 (10 mL) and pyridine (10 mL) was stirred overnight at ambient temperature. After addition of water, the resulting mixture was extracted with Et_2O, and the crude product was purified as described above for **22b** to furnish **22c**[18] (1.00 g, 87% yield): ^1H NMR δ 2.05−2.16 (m, 2 H), 2.46 (dt, J = 4.5, 6 Hz, 2 H), 2.67 (t, J = 7 Hz, 2 H), 7.79 (t, J = 4.5 Hz, 1 H).

2-Iodo-4-[(1-methyl-1-triethylsilyloxy)ethyl]-3-phenyl-1-cyclohexanone (23a). To a suspension of CuCN (68 mg, 0.76 mmol) in Et_2O (5 mL) at −78 °C was added PhLi (1.62 mL, 1.0 M in cyclohexanes−Et_2O, 1.62 mmol). After the addition, the reaction mixture was stirred at 0 °C for 10 min, cooled to −78 °C, and stirred further for 30 min. To the resulting pale yellow solution of cuprate **10a** was added slowly a solution of 2-iodocyclohexenone **22a** (200 mg, 0.507 mmol) and $BF_3{\cdot}Et_2O$ (0.063 mL, 0.502 mmol) in Et_2O (5 mL) at −78 °C. After 2 h at −78 °C, the solution was poured into saturated NH_4Cl, and the product was extracted with EtOAc twice. The combined organic extracts were dried and concentrated to afford an oily residue, which was purified by chromatography (hexane/EtOAc) to furnish **23a** (156 mg, 65% yield): IR (neat) 1712, 1455 cm^{-1}; ^1H NMR δ 0.50−0.70 (m, 6 H), 0.8−1.2 (m, 15 H), 2.20−3.15 (m, 5 H), 3.58−3.72 (m, 1 H), 4.61 (d, J = 6 Hz, 0.5 H) and 5.44 (d, J = 6 Hz, 0.5 H), 7.05−7.40 (m, 5 H). Anal. Calcd for $C_{21}H_{33}IO_2Si$: C, 53.38; H, 7.04. Found: C, 53.17; H, 6.94.

3-[(2,6-Bis(methoxymethoxy)-4-pentyl)phenyl]-2-iodo-4-[(1-methyl-1-triethylsilyloxy)ethyl]-1-cyclohexanone (23b). To an ice-cold solution of the bis MOM ether of olivetol (1.02 g, 3.80 mmol) in Et_2O (5 mL) was added *n*-BuLi (1.93 mL, 2.30 M in hexane, 4.44 mmol) over 10 min. The mixture was stirred at 0 °C for 10 min and then at ambient temperature for 2 h. In a separate flask was taken Et_2O (5 mL) and CuCN (170 mg, 1.90 mmol), and the mixture was cooled to −78 °C. The lithiated olivetol solution was transferred to the copper suspension over 10 min at −78 °C. After the addition, the reaction mixture was stirred at 0 °C for 10 min, cooled to −78 °C, and stirred further for 30 min. To the resulting pale yellow solution of cuprate **10b** was added slowly a solution of iodoenone **22a** (500 mg, 1.27 mmol) and $BF_3{\cdot}Et_2O$ (0.159 mL, 1.27 mmol) in Et_2O (5 mL) at −78 °C. After 2 h at −78 °C, the solution was poured into saturated NH_4Cl, and the product was extracted with EtOAc twice. The combined organic extracts were dried and evaporated to afford an oily residue, which was purified by chromatography (hexane/EtOAc) to furnish **23b** (605 mg, 72% yield): IR (neat) 1725, 1611, 1583 cm^{-1}; ^1H NMR δ 0.57−0.67 (m, 6 H), 0.88 (t, J = 7 Hz, 3 H), 0.97 (t, J = 8 Hz, 9 H), 1.26 (s, 3 H), 1.27−1.35 (m, 4 H), 1.37 (s, 3 H), 1.52−1.68 (m, 2 H), 1.96−2.21 (m, 3 H), 2.47−2.62 (m, 3 H), 2.81 (dt, J = 18, 7 Hz, 1 H), 3.42 (s, 3 H), 3.50 (s, 3 H), 4.53 (dd, J = 9, 5 Hz, 1 H), 4.80 (d, J = 7 Hz, 1 H), 5.01 (d, J = 7 Hz, 1 H), 5.20 (s, 2 H), 5.71 (d, J = 9 Hz, 1 H), 6.62 (d, J = 1 Hz, 1 H), 6.66 (d, J = 1 Hz, 1 H); ^{13}C NMR δ 6.9, 7.3, 14.2, 22.6, 22.9, 28.7, 30.0, 31.0, 31.8, 36.4, 36.8, 41.1, 43.1, 50.9, 56.2, 56.4, 60.5, 94.3, 94.9, 107.8, 108.0, 119.7, 143.9, 155.2, 156.3, 202.2. Anal. Calcd for $C_{30}H_{51}IO_6Si$: C, 54.37; H, 7.76. Found: C, 54.20; H, 7.96.

Phosphate 12a. By using the procedure for synthesis of **12b** (below), iodoketone **23a** (150 mg, 0.317 mmol) in THF (5 mL), EtMgBr (0.48 mL, 1.0 M in THF, 0.48 mmol), and $ClP(O)(OEt)_2$ (0.114 mL, 0.792 mmol) afforded the title product **12a** (97 mg, 63% yield) after purification by chromatography: IR (neat) 1687, 1456, 1270 cm^{-1}; ^1H NMR δ 0.50−0.65 (m, 6 H), 0.90−1.02 (m, 9 H), 1.13−1.36 (m, 12 H), 1.64−1.88 (m, 2 H), 1.90−2.06 (m, 1 H), 2.28−2.53 (m, 2 H), 3.66 (d, J = 2 Hz, 1 H), 4.04−4.20 (m, 4 H), 5.32−5.40 (m, 1 H), 7.10−7.34 (m, 5 H). Anal. Calcd for $C_{25}H_{43}O_5PSi$: C, 62.21; H, 8.98. Found: C, 61.89; H, 8.65.

Phosphate 12b. To an ice-cold solution of iodoketone **23b** (561 mg, 0.847 mmol) in THF (10 mL) was added EtMgBr (1.27 mL, 1.0 M in THF, 1.27 mmol). After 10 min of stirring, $ClP(O)(OEt)_2$ (0.31 mL, 2.15 mmol) was added to the resulting pale yellow solution. The reaction was continued at 0 °C for 2 h and quenched with saturated $NaHCO_3$. The product was extracted with EtOAc twice. The combined organic extracts were dried and concentrated to afford an oily residue, which was purified by chromatography (hexane/EtOAc) on silica gel that was pretreated with Et_3N (5wt %) to furnish **12b** (404 mg, 71% yield): IR (neat) 1608, 1580 cm^{-1}; ^1H NMR δ 0.46−0.56 (m, 6 H), 0.86−0.96 (m, 15 H), 1.12 (s, 3 H), 1.24−1.36 (m, 10 H), 1.50−1.70 (m, 3 H), 2.20−2.55 (m, 6 H), 3.48 (br s, 6 H), 4.02−4.16 (m, 5 H), 5.06−5.18 (m, 5 H), 6.57 (s, 2 H); ^{13}C NMR δ 6.9, 7.3, 14.2, 16.1 (d, J = 7 Hz), 22.6, 25.3, 26.3, 28.3 (d, J = 3 Hz), 30.1, 31.1, 31.7, 32.8, 36.3, 46.9, 56.1, 63.84, 63.87, 63.92, 63.95 (four peaks for two carbons (2 CH_2)), 76.1, 94.8, 108.1, 108.7, 115.1 (d, J = 6 Hz), 120.8, 142.5, 147.0 (d, J = 15 Hz), 154.7 (br s), 156.8 (br s). Anal. Calcd for $C_{34}H_{61}O_9PSi$: C, 60.69; H, 9.14. Found: C, 60.68; H, 9.06.

Phosphate 12d. According to the procedure for synthesis of **23b**, cuprate **10d** was prepared from the bis SEM ether of olivetol (601 mg, 1.36 mmol) in Et_2O (5 mL), *n*-BuLi (0.64 mL, 2.50 M in hexane, 1.60 mmol), and CuCN (61 mg, 0.68 mmol) in Et_2O (5 mL) and submitted to reaction with a solution of enone **22a** (180 mg, 0.456 mmol) and $BF_3{\cdot}Et_2O$ (0.068 mL, 0.547 mmol) in E_2O (5 mL) at −78 °C to afford a mixture (252 mg) of **23d** and the bis SEM ether of olivetol, which was taken for the next step after semi purification by fast column chromatography on silica gel. Spectral data of **23d**: ^1H NMR δ 0.05 (s, 18 H), 0.65 (q, J = 8 Hz, 6 H), 0.85−1.05 (m, 16 H), 1.25 (s, 3 H), 1.20−1.40 (m, 2 H), 1.37 (s, 3 H), 1.50−1.65 (m, 3 H), 1.90−2.20 (m, 3 H), 2.45−2.60 (m, 4 H), 2.83 (dt, J = 7, 18 Hz, 1 H), 3.60−3.85 (m, 4 H), 4.52 (dd, J = 9, 5 Hz, 1 H), 4.87 (d, J = 7 Hz, 1 H), 5.02 (d, J = 7 Hz, 1 H), 5.24 (s, 2 H), 5.72 (d, J = 9 Hz, 1 H), 6.65 (s, 1 H), 6.72 (s, 1 H).

By using the procedure for synthesis of **12b**, iodoketone **23d** (252 mg) in THF (5 mL), EtMgBr (0.45 mL, 1.0 M in THF, 0.45 mmol), and $ClP(O)(OEt)_2$ (0.11 mL, 0.76 mmol) afforded the title product **12d** (205 mg, 53% yield from **22a**) after purification by chromatography: IR (neat) 1580 cm^{-1}; ^1H NMR δ 0.00 (s, 18 H), 0.46−0.55 (m, 6 H), 0.82−1.02 (m, 19 H), 1.10 (s, 3 H), 1.22−1.34 (m, 11 H), 1.48−1.65 (m, 3 H), 2.17−2.43 (m, 3 H), 2.49 (t, J = 8 Hz, 2 H), 3.72 (br s, 4 H), 4.00−4.15 (m, 5 H), 5.03 (dd, J = 5, 3 Hz, 1 H), 5.06−5.24 (m, 4 H), 6.60 (s, 2 H); ^{13}C NMR δ −1.2, 7.0, 7.4, 14.3, 16.2 (d, J = 7 Hz), 18.2, 22.7, 25.3, 26.2, 28.3 (d, J = 3 Hz), 30.4, 31.2, 31.8, 32.8, 36.3, 47.1, 63.9 (d, J = 6 Hz), 66.1, 76.1, 93.4, 108.0, 108.9, 115.3 (d, J = 6 Hz), 120.6, 142.5, 147.1 (d, J = 9 Hz), 154.9 (br s), 157.2 (br s). Anal. Calcd for $C_{42}H_{81}O_9PSi_3$: C, 59.68; H, 9.66. Found: C, 59.60; H, 9.94.

3-[(2,6-Bis(methoxymethoxy)-4-pentyl)phenyl]-2-[(1-hydroxy-3-phenyl)propyl]-4-[(1-methyl-1-triethylsilyloxy)-ethyl]-1-cyclohexanone (28). To an ice-cold solution of iodoketone **23b** (50 mg, 0.075 mmol) in THF (2 mL) was added EtMgBr (0.091 mL, 1.0 M in THF, 0.091 mmol). After 10 min of stirring, $Ph(CH_2)_2CHO$ (**27**) (0.014 mL, 0.106 mmol) was added to the resulting pale yellow solution. The reaction was continued at 0 °C for 2 h and quenched with saturated

$NaHCO_3$. The product was extracted with EtOAc twice. The combined organic extracts were dried and concentrated to afford an oily residue, which was purified by chromatography (hexane/EtOAc) to furnish aldol **28** (40 mg, 79% yield): IR (neat) 3515, 1683, 1609, 1581 cm^{-1}; ^1H NMR δ 0.47−0.68 (m, 6 H), 0.80−1.10 (m, 13 H), 1.02 (s, 3 H), 1.14 (s, 3 H), 1.20−2.00 (m, 9 H), 2.25−2.64 (m, 6 H), 2.82−3.03 (m, 1 H), 3.09−3.31 (m, 2 H), 3.35 (s, 3 H), 3.48 (s, 3 H), 3.33−3.52 (m, 1 H), 3.68 (t, J = 9 Hz, 1 H), 4.93 (d, J = 7 Hz, 1 H), 5.02−5.26 (m, 4 H), 6.60 (s, 2 H), 7.07−7.32 (m, 5 H). HRMS (CI) m/z calcd for $C_{39}H_{62}O_7Si$ (M^+) 670.4265, found 670.4266.

3-[(2,6-Bis(methoxymethoxy)-4-pentyl)phenyl]-2-hydroxymethyl-4-[(1-methyl-1-triethylsilyloxy)ethyl]-1-cyclohexanone (29). To an ice-cold solution of iodoketone **23b** (220 mg, 0.332 mmol) in THF (2 mL) was added EtMgBr (0.50 mL, 1.0 M in THF, 0.50 mmol). After 10 min of stirring, gaseous CH_2O in THF (5 mL) freshly prepared by cracking $(CH_2O)_n$ (200 mg, 6.6 mmol) was added to the resulting pale yellow solution. The reaction was continued at 0 °C for 2 h and quenched with saturated $NaHCO_3$. The product was extracted with EtOAc twice. The combined organic extracts were dried and concentrated to afford an oily residue, which was purified by chromatography (hexane/EtOAc) to furnish aldol **29** (120 mg, 64% yield): IR (neat) 3567, 1700 cm^{-1}; ^1H NMR (diagnostic signals) δ 0.51−0.65 (m, 6 H), 1.05 (s, CH_3), 1.11 (s, CH_3), 3.43 and 3.50 (2s, minor isomer, 2 CH_3), 3.47 and 3.50 (2s, major isomer, 2 CH_3). HRMS (CI) m/z calcd for $C_{31}H_{54}O_7Si$ (M^+) 566.3639, found 566.3638.

3-[(2,6-Bis(methoxymethoxy)-4-pentyl)phenyl]-2-methylene-4-[(1-methyl-1-triethylsilyloxy)ethyl]-1-cyclohexanone (30). To an ice-cold solution of aldol **29** (50 mg, 0.088 mmol) and Et_3N (0.12 mL, 0.88 mmol) in CH_2Cl_2 (2 mL) was added MsCl (0.054 mL, 0.698 mmol). After 1 h of stirring at 0 °C, the reaction was quenched with $NaHCO_3$ and the product was extracted with EtOAc twice. The combined organic extracts were dried and concentrated to afford an oily residue, which was purified by chromatography (hexane/EtOAc) to furnish the corresponding mesylate (44 mg, 79% yield): IR (neat) 1715, 1357 cm^{-1}; ^1H NMR δ 0.51−0.63 (m, 6 H), 0.84−1.00 (m, 12 H), 1.05 (s, 3 H), 1.13 (s, 3 H), 1.23−1.42 (m, 4 H), 1.50−1.66 (m, 2 H), 1.83−1.98 (m, 1 H), 2.30−2.75 (m, 6 H), 2.97 (s, 3 H), 3.39−3.52 (m, 1 H), 3.47 (s, 3 H), 3.50 (s, 3 H), 3.73 (dd, J = 12, 8 Hz, 1 H), 4.02 (dd, J = 10, 3 Hz, 1 H), 4.14 (dd, J = 10, 6 Hz, 1 H), 5.16 (s, 2 H), 5.23 (s, 2 H), 6.60 (br s, 1 H), 6.67 (d, J = 1 Hz, 1 H); ^{13}C NMR δ 6.8, 7.3, 14.3, 22.7, 24.1, 27.3, 30.2, 31.1, 31.9, 34.7, 36.5, 36.8, 38.9, 49.3, 50.0, 56.3, 56.6, 67.8, 76.8, 94.3, 95.2, 107.85, 107.92, 117.3, 144.0, 155.4, 156.3, 211.0. HRMS (CI) m/z calcd for $C_{32}H_{56}O_9SSi$ (M^+) 644.3414, found 644.3408.

To an ice-cold solution of the above mesylate (40 mg, 0.062 mmol) in CH_2Cl_2 (2 mL) was added Al_2O_3 (63 mg, 0.62 mmol).[46] After stirring overnight at ambient temperature, the reaction mixture was filtered through a pad of Celite and the solvent was evaporated under reduced pressure to afford an oily residue, which was purified by chromatography (hexane/EtOAc) to furnish **30** (30 mg, 88% yield): IR (neat) 1721, 1697, 1608 cm^{-1}; ^1H NMR δ 0.55 (q, J = 8 Hz, 6 H), 0.85−0.97 (m, 12 H), 1.14 (s, 3 H), 1.23 (s, 3 H), 1.2−1.4 (m, 4 H), 1.49−1.82 (m, 3 H), 2.04−2.27 (m, 2 H), 2.39−2.69 (m, 4 H), 3.39 (br s, 3 H), 3.50 (br s, 3 H), 4.61 (d, J = 7 Hz, 1 H), 5.00 (br s, 2 H), 5.08 (t, J = 1.5 Hz, 1 H), 5.21 (br s, 2 H), 5.79 (t, J = 1.5 Hz, 1 H), 6.58 (br s, 2 H); ^{13}C NMR δ 6.9, 7.4, 14.3, 22.7, 22.8, 27.4, 30.0, 31.2, 31.8, 36.4, 36.9, 37.9, 49.7, 56.3, 76.3, 94.0, 94.7, 107.7, 108.0, 121.3, 122.5, 142.9, 149.0, 154 (br s), 155 (br s), 202.6. HRMS (CI) m/z calcd for $C_{31}H_{52}O_6Si$ (M^+) 548.3533, found 548.3530.

1-Methyl-4-[(1-methyl-1-triethylsilyloxy)ethyl]-3-phenyl-1-cyclohexene (31a). According to the procedure for synthesis of **31b** (below), methylation of enol phosphate **12a** (90 mg, 0.186 mmol) in THF (2 mL) was carried out with MeMgCl (0.17 mL, 2.80 M in THF, 0.48 mmol) and $Ni(acac)_2$ (5 mg, 0.019 mmol) in THF (2 mL) to afford **31a** (60 mg, 94% yield): IR (neat) 1601, 1456 cm^{-1}; ^1H NMR δ 0.55 (q, J = 8 Hz, 6 H), 0.94 (t, J = 8 Hz, 9 H), 1.05 (s, 3 H), 1.13 (s, 3 H), 1.49−1.64 (m, 1 H), 1.68 (s, 3 H), 1.73−1.85 (m, 1 H), 1.87−2.06 (m, 3 H), 3.39−3.47 (m, 2 H), 5.21 (br s, 1 H), 7.09−7.32 (m, 5 H); ^{13}C NMR δ 7.0, 7.4, 22.6, 23.7, 28.6, 29.5, 30.0, 43.9, 51.3, 76.3, 125.5, 125.8, 128.2, 128.3, 133.3, 148.6. Anal. Calcd for $C_{22}H_{36}OSi$: C, 76.68; H, 10.53. Found: C, 76.66; H, 10.56.

3-[(2,6-Bis(methoxymethoxy)-4-pentyl)phenyl]-1-methyl-4-[(1-methyl-1-triethylsilyloxy)ethyl]-1-cyclohexene (31b). To an ice-cold solution of $Ni(acac)_2$ (8 mg, 0.03 mmol) in THF (5 mL) was added MeMgCl (0.27 mL, 2.80 M in THF, 0.76 mmol). After 10 min at 0 °C, a solution of enol phosphate **12b** (200 mg, 0.297 mmol) in THF (5 mL) was added. The solution was stirred at ambient temperature overnight and diluted with saturated $NaHCO_3$ at 0 °C. The product was extracted with EtOAc twice. The combined organic layers were dried and concentrated to afford an oily residue, which was purified by chromatography (hexane/EtOAc) to furnish **31b** (146 mg, 92% yield): IR (neat) 1608, 1579 cm^{-1}; ^1H NMR δ 0.44−0.55 (m, 6 H), 0.85−0.96 (m, 15 H), 1.11 (s, 3 H), 1.22−1.64 (m, 10 H), 1.84−2.20 (m, 3 H), 2.38−2.54 (m, 3 H), 3.46 (br s, 6 H), 3.93 (d, J = 9 Hz, 1 H), 4.96−5.15 (m, 5 H), 6.57 (s, 2 H); ^{13}C NMR δ 7.0, 7.4, 14.3, 22.7, 23.5, 25.4, 26.4, 30.1, 30.9, 31.2, 31.9, 34.6, 36.4, 47.3, 56.1 (br s), 76.6, 94.3, 95.0, 108.4, 108.9, 122.9, 125.7, 132.3, 142.0, 154.8 (br s), 156.5 (br s). Anal. Calcd for $C_{31}H_{54}O_5Si$: C, 69.62; H, 10.18. Found: C, 69.20; H, 10.09.

3-[(2,6-Bis(methoxymethoxy)-4-pentyl)phenyl]-1-[(dimethyl(propyloxy)silyl)methyl]-4-[(1-methyl-1-triethylsilyloxy)ethyl]-1-cyclohexene (33b). To an ice-cold solution of $Ni(acac)_2$ (0.10 mg, 0.039 mmol) in THF (5 mL) was added $ClMgCH_2Si(Me)_2(OPr\text{-}i)$ (1.01 mL, 0.95 M in THF, 0.96 mmol). After 10 min of stirring at 0 °C, a solution of enol phosphate **12b** (260 mg, 0.386 mmol) in THF (5 mL) was added and stirring was continued overnight at ambient temperature. The reaction was cooled to 0 °C and quenched with saturated $NaHCO_3$. The product was extracted with EtOAc twice. The combined organic layers were dried and concentrated to afford an oily residue, which was purified by chromatography (hexane/EtOAc) to furnish **33b** (220 mg, 88% yield): IR (neat) 1608, 1579 cm^{-1}; ^1H NMR δ 0.09 and 0.10 2s, 6 H), 0.45−0.56 (m, 6 H), 0.85−0.97 (m, 15 H), 1.07−1.18 (m, 9 H), 1.25−1.64 (m, 9 H), 1.88−2.18 (m, 3 H), 2.37−2.56 (m, 3 H), 3.46 (s, 3 H), 3.48 (s, 3 H), 3.89−4.04 (m, 2 H), 4.86 (s, 1 H), 5.02−5.26 (m, 4 H), 6.57 (s, 2 H); ^{13}C NMR δ −1.1, −1.0, 7.0, 7.4, 14.3, 22.7, 25.6, 25.9, 26.6, 27.3, 30.1, 31.2, 31.6, 31.9, 34.6, 36.3, 47.1, 56.0, 56.2, 64.9, 76.5, 94.4, 95.1, 108.5, 108.9, 123.0, 124.3, 132.4, 141.8, 154.8, 156.6. Anal. Calcd for $C_{36}H_{66}O_6Si_2$: C, 66.41; H, 10.22. Found: C, 66.13; H, 10.11.

3-[(2,6-Dimethoxy-4-pentyl)phenyl]-1-[(dimethyl(propyloxy)silyl)methyl]-4-[(1-methyl-1-triethylsilyloxy)ethyl]-1-cyclohexene (33c). According to the procedure for synthesis of **33b**, the silylmethylation of enol phosphate **12c** (350 mg, 0.571 mmol) in THF (5 mL) was carried out with $ClMgCH_2Si(Me)_2(OPr\text{-}i)$ (1.32 mL, 1.08 M in THF, 1.43 mmol) and $Ni(acac)_2$ (15 mg, 0.058 mmol) in THF (5 mL) to afford **33c** (286 mg, 85% yield): IR (neat) 1607, 1579, 1456 cm^{-1}; ^1H NMR δ 0.06 (s, 3 H), 0.12 (s, 3 H), 0.45−0.54 (m, 6 H), 0.85−0.95 (m, 15 H), 1.05 (br s, 3 H), 1.11 (d, J = 6 Hz, 3 H), 1.12 (d, J = 6 Hz, 3 H), 1.27−1.67 (m, 9 H), 1.81−1.94 (m, 1 H), 2.03−2.23 (m, 2 H), 2.32−2.45 (m, 1 H), 2.53 (t, J = 8 Hz, 2 H), 3.70 (br s, 3 H), 3.77 (br s, 3 H), 3.88−3.97 (m, 2 H), 4.83 (br s, 1 H), 6.47 (br s, 2 H); ^{13}C NMR δ −1.4, −0.9, 7.0, 7.4, 14.3, 22.8, 25.7, 26.0, 26.4, 27.8, 30.1, 31.3, 31.8, 31.9, 34.2, 36.6, 46.8, 55.3, 55.9, 64.9, 76.6, 104.1, 104.7, 121.1, 124.4, 132.3, 141.5, 157.0, 158.8. Anal. Calcd for $C_{34}H_{62}O_4Si_2$: C, 69.09; H, 10.57. Found: C, 69.04; H, 10.22.

3-[(2,6-Bis(methoxymethoxy)-4-pentyl)phenyl]-1-hydroxymethyl-4-[(1-methyl-1-triethylsilyloxy)ethyl]-1-cyclohexene (34b). To a solution of **33b** (200 mg, 0.307 mmol), $NaHCO_3$ (103 mg, 1.23 mmol), and KF (124 mg, 2.13 mmol) in THF/MeOH (1:1) (5 mL) was added 35% H_2O_2 (0.24 mL,

2.74 mmol). The reaction mixture was stirred at 50 °C for 4 h, cooled to 0 °C, and poured into saturated $Na_2S_2O_3$. The resulting mixture was stirred vigorously at ambient temperature for 1 h and diluted with EtOAc. The organic layer was separated, and the aqueous layer was extracted with EtOAc twice. The combined organic layers were dried and concentrated to afford an oily residue, which was purified by chromatography (hexane/EtOAc) to furnish **34b** (98 mg, 58% yield: IR (neat) 3420, 1608, 1433 cm^{-1}; ^1H NMR δ 0.51 (q, J = 8 Hz, 6 H), 0.86−0.98 (m, 15 H), 1.12 (s, 3 H), 1.20−1.70 (m, 8 H), 2.02−2.28 (m, 3 H), 2.37−2.56 (m, 3 H), 3.46 (s, 6 H), 3.93−4.04 (m, 3 H), 4.97−5.24 (m, 4 H), 5.28 (s, 1 H), 6.47−6.64 (m, 2 H); ^{13}C NMR δ 7.0, 7.4, 14.3, 22.7, 25.2, 26.4, 26.6, 30.0, 31.2, 31.9, 34.2, 36.4, 47.8, 56.3, 67.7, 76.4, 94.6, 95.0, 108.4, 108.8, 122.0, 127.9, 136.1, 142.4, 154.9, 156.5. Anal. Calcd for $C_{31}H_{54}O_6Si$: C, 67.59; H, 9.88. Found: C, 67.34; H, 9.80.

3-[(2,6-Dimethoxy-4-pentyl)phenyl]-1-hydroxymethyl-4-[(1-methyl-1-triethylsilyloxy)ethyl]-1-cyclohexene (34c). According to the preceding procedure, a mixture of **33c** (250 mg, 0.423 mmol), 35% H_2O_2 (0.33 mL, 3.8 mmol), $NaHCO_3$ (142 mg, 1.69 mmol), and KF (171 mg, 2.95 mmol) in THF/MeOH (1:1) (5 mL) was stirred at 50 °C for 4 h to afford **34c** (107 mg, 52% yield) after chromatography on silica gel (hexane/EtOAc): IR (neat) 3361, 1607, 1578, 1458 cm^{-1}; ^1H NMR δ 0.51 (q, J = 8 Hz, 6 H), 0.87−0.95 (m, 15 H), 1.06 (s, 3 H), 1.20−2.51 (m, 5 H), 1.54−1.68 (m, 3 H), 2.03−2.25 (m, 3 H), 2.39 (ddd, J = 13, 10, 3 Hz, 1 H), 2.54 (t, J = 8 Hz, 2 H), 3.75 (br s, 6 H), 3.97 (br s, 3 H), 5.24 (br s, 1 H), 6.33 (m, 2 H); ^{13}C NMR δ 7.0, 7.4, 14.3, 22.8, 25.2, 26.2, 26.7, 30.0, 31.3, 31.9, 33.6, 36.6, 47.4, 55.7 (br s), 67.7, 76.5, 104.2 (br s), 105.2 (br s), 120.5, 127.8, 136.1, 141.9, 156.9 (br s), 158.8 (br s). Anal. Calcd for $C_{29}H_{50}O_4Si$: C, 70.97; H, 10.27. Found: C, 70.72; H, 9.96.

6,6-Dimethylnorpinan-2-one (44). A stream of ozonized oxygen was gently bubbled into a solution of (+)-β-pinene (**43**) (2.00 g, 12.7 mmol) in MeOH (30 mL) at −78 °C for 2.5 h. Argon was then bubbled to the solution at −78 °C to remove excess of O_3, and the reaction was quenched with $(CH_3)_2S$ (1.60 mL, 22.0 mmol) at −78 °C. The solution was warmed to ambient temperature, stirred overnight, and diluted with H_2O. The product was extracted with EtOAc twice. The combined organic layers were washed with H_2O and brine, dried, and concentrated to afford an oily residue, which was purified by chromatography (hexane/EtOAc) to furnish **44** (1.57 g, 78% yield): $[\alpha]^{28}_D$ −33 (*c* 0.56, MeOH); lit.[42] $[\alpha]^{22}_D$ +36.5 (*c* 4.0, MeOH) for the enantiomer; updated ^1H NMR δ 0.80 (s, 3 H), 1.28 (s, 3 H), 1.54 (d, J = 10 Hz, 1 H), 1.83−2.07 (m, 2 H), 2.14−2.36 (m, 2 H) 2.42−2.60 (m, 3 H).

(*R*)-4-[(1-Acetoxy-1-methyl)ethyl]-2-cyclohexenone (46). The procedure for synthesis of the enantiomer of **46** reported by Razdan[44] was followed. Briefly, a solution of **44** (1.20 g, 8.68 mmol), $BF_3{\cdot}OEt_2$ (0.76 mL, 6.05 mmol), and $Zn(OAc)_2$ (2.70 g, 14.7 mmol) in Ac_2O (20 mL) was stirred at 0 °C for 3 h and poured into a 1:1 mixture of ice and Et_2O. After 30 min of vigorous stirring, the organic layer was separated, and the aqueous layer was extracted with Et_2O twice. The combined organic layers were stirred with saturated $NaHCO_3$ to neutralize the solution, washed with H_2O and brine, dried, and concentrated to afford a oily residue, which was purified by chromatography (hexane/EtOAc) to furnish **45** (1.50 g, 72% yield): $[\alpha]^{26}_D$ +45 (*c* 0.47, EtOH); lit.[44a] $[\alpha]^{29.5}_D$ −48.3 (*c* 0.0325, EtOH) for the enantiomer. The ^1H NMR (300 MHz) spectrum of **45** was identical with the ^1H NMR (400 MHz) data reported in lit.[44a] Additional data of **45**: IR (neat) 3440, 1756, 1730 cm^{-1}; ^{13}C NMR δ 20.8, 22.2, 23.0, 23.2, 23.3, 24.4, 27.1, 42.0, 83.8, 112.8, 147.8, 168.8, 169.8.

To a solution of $Pd(OAc)_2$ (67 mg, 0.299 mmol), **45** (1.44 g, 5.99 mmol), DPPE (119 mg, 0.299 mmol), and allyl ethyl carbonate (1.57 mL, 11.9 mmol) in MeCN (20 mL) was added Bu_3SnOMe (0.34 mL, 1.18 mmol). The reaction mixture was stirred at 80 °C for 5 h, cooled to 0 °C, and poured into a 1:1 mixture of brine and Et_2O. The reaction mixture was filtered through a pad of Celite. The organic layer was separated, and the aqueous layer was extracted with Et_2O twice. The combined organic layers were washed with saturated $NaHCO_3$, dried, and concentrated to afford an oily residue, which was purified by chromatography (hexane/EtOAc) to furnish **46** (1.00 g, 85% yield): $[\alpha]^{26}_D$ +42 (*c* 0.41, EtOH); lit.[44a] $[\alpha]^{27}_D$ −49 (*c* 0.06015, EtOH) for the enantiomer. The ^1H NMR (300 MHz) spectrum of **46** was identical with the ^1H NMR (400 MHz) data reported in lit.[44a] Additional data of **46**: IR (neat) 1731, 1682 cm^{-1}; ^{13}C NMR δ 22.3, 23.2, 23.6, 24.2, 37.2, 44.8, 83.0, 130.1, 150.0, 169.9, 198.7.

(*R*)-4-[(1-Hydroxy-1-methyl)ethyl]-2-cyclohexen-1-one (48). To a solution of enone **46** (1.00 g, 5.10 mmol) in THF (20 mL) at −78 °C was added DIBAL (29.8 mL, 0.95 M in hexane, 28.3 mmol). The reaction was carried out at −78 °C for 1.5 h and was quenched with THF/H_2O (1:1, 20 mL). After 1 h of stirred at ambient temperature, NaF (3.0 g) was added to the reaction mixture. The resulting mixture was stirred for additional 1 h and filtered through a pad of Celite. The filtrate was concentrated to afford an oily residue, which was purified by chromatography (CH_2Cl_2/acetone) to furnish diol **47** (750 mg, 94% yield): IR (Nujol) 3290 cm^{-1}; ^1H NMR δ 1.05 (s, 3 H), 1.11 (s, 3 H), 1.70−1.86 (m, 2 H), 1.90−2.20 (m, 3 H), 2.38 (br s, 1 H), 3.20 (br s, 1 H), 4.12 (br s, 1 H), 5.65−5.80 (m, 2 H).

A mixture of diol **47** (400 mg, 2.56 mmol), PCC (662 mg, 3.07 mmol), and Celite (2.5 g) in CH_2Cl_2 (10 mL) was stirred for 2 h at ambient temperature and filtered through a pad of Celite. The filtrate was concentrated under reduced pressure to afford a crude mixture, which was purified by chromatography (CH_2Cl_2/acetone) to furnish **48** (300 mg, 76% yield): $[\alpha]^{29}_D$ +72 (*c* 0.44, MeOH); lit.[44b] $[\alpha]^{22}_D$ +58.76 (*c* 0.0573, MeOH). The spectral data of **48**: IR (neat) 3430, 1668 cm^{-1}; ^1H NMR δ 1.22 (s, 3 H), 1.31 (s, 3 H), 1.68−1.85 (m, 1 H), 2.10−2.21 (m, 1 H), 2.30−2.62 (m, 4 H), 6.08 (ddd, J = 11, 3, 1 Hz, 1 H), 7.20 (dt, J = 11, 2 Hz, 1 H); ^{13}C NMR δ 24.7 26.0, 28.3, 37.4, 47.9, 72.0, 129.9, 152.2, 199.9.

(*R*)-4-[(1-Methyl-1-triethylsilyloxy)ethyl]-2-cyclohexen-1-one ((+)-5a). A solution of alcohol **48** (300 mg, 1.94 mmol), TESCl (0.50 mL, 2.94 mmol), and imidazole (238 mg, 3.50 mmol) in DMF (5 mL) was stirred overnight at ambient temperature and diluted with saturated $NaHCO_3$ and hexane (1:1) at 0 °C. The organic layer was separated, and the aqueous layer was extracted with hexane twice. The combined organic extracts were dried and concentrated under reduced pressure to afford an oily residue, which was purified by chromatography (hexane/EtOAc) to furnish (+)-**5a** (443 mg, 85% yield): $[\alpha]^{24}_D$ +67 (*c* 0.49, MeOH).

(*R*)-2-Iodo-4-[1-methyl-1-(triethylsilyloxy)ethyl]-2-cyclohexen-1-one ((−)-22a). The procedure described for synthesis of racemic **22a** (vide supra) was repeated with enone **5a** (500 mg, 1.86 mmol) in CCl_4 (5 mL) and pyridine (5 mL), a solution of I_2 (1.42 g, 5.59 mmol) dissolved in CCl_4 and pyridine (1:1, 10 mL) to afford (−)-**22a** (537 mg, 73% yield) after chromatography (hexane/EtOAc): $[\alpha]^{28}_D$ −5 (*c* 0.96, MeOH).

(*R*)-3-[(2,6-Dimethoxy-4-pentyl)phenyl]-2-iodo-4-[(1-methyl-1-triethylsilyloxy)ethyl]-1-cyclohexanone ((+)-23c). According to the procedure for synthesis of **23b**, cuprate **10c** was prepared from the bis methyl ether of olivetol (850 mg, 4.08 mmol) in Et_2O (5 mL), *n*-BuLi (1.73 mL, 2.51 M in hexane, 4.34 mmol), CuCN (182 mg, 2.04 mmol) in Et_2O (5 mL), and submitted to the reaction with a solution of enone (−)-**22a** (537 mg, 1.35 mmol) and $BF_3{\cdot}Et_2O$ (0.17 mL, 1.35 mmol) in Et_2O (5 mL) to afford (+)-**23c** (510 mg, 62% yield) after purification by chromatography (hexane/EtOAc): $[\alpha]^{30}_D$ +37 (*c* 0.44, $CHCl_3$).

Phosphate (−)-12c. By using the procedure for synthesis of **12b**, iodoketone (+)-**23c** (240 mg, 0.398 mmol) in THF (5 mL), EtMgBr (0.60 mL, 1.0 M in THF, 0.59 mmol), and ClP(O)$(OEt)_2$ (0.145 mL, 0.991 mmol) afforded (−)-**12c** (161 mg,

66% yield) after purification by chromatography: $[\alpha]^{30}_D$ −43 (*c* 0.53, $CHCl_3$).

(3*R*,4*R*)-3-[(2,6-Dimethoxy-4-pentyl)phenyl]-1-methyl-4-[(1-methyl-1-triethylsilyloxy)ethyl]-1-cyclohexene ((−)-31c). According to the procedure for synthesis of **31b**, methylation of enol phosphate (−)-**12c** (140 mg, 0.228 mmol) in THF (2 mL) was carried out with MeMgCl (0.16 mL, 2.80 M in THF, 0.45 mmol) and $Ni(acac)_2$ (6 mg, 0.023 mmol) in THF (2 mL) to afford (−)-**31c** (100 mg, 93% yield): $[\alpha]^{28}_D$ −84 (*c* 0.49, $CHCl_3$).

(3*R*,4*R*)-3-[(2-Hydroxy-6-methoxy-4-pentyl)phenyl]-1-methyl-4-[(1-methyl-1-triethylsilyloxy)ethyl]-1-cyclohexene ((−)-38). To a solution of (−)-**31c** (100 mg, 0.211 mmol) in DMF (2 mL) was added NaSEt (265 mg, 80% content, 2.52 mmol). After stirring for 12 h at 140 °C, the mixture was cooled to 0 °C and diluted with saturated $NaHCO_3$. The product was extracted with Et_2O twice. The combined organic layers were dried and concentrated to afford an oily residue, which was purified by chromatography (hexane/EtOAc) to furnish (−)-**38** (53 mg, 73% yield): $[\alpha]^{26}_D$ −44 (*c* 0.20, $CHCl_3$); IR (Nujol) 3524, 3209 cm^{-1}; ^1H NMR δ 0.89 (t, J = 7 Hz, 3 H), 1.12 (s, 3 H), 1.14 (s, 3 H), 1.25−1.40 (m, 4 H), 1.44−1.69 (m, 3 H), 1.75 (s, 3 H), 1.90−2.27 (m, 5 H), 2.50 (t, J = 8 Hz, 2 H), 3.82 (br s, 3 H), 4.03 (br s, 1 H), 5.41 (br s, 1 H), 6.03 (br s, 1 H), 6.29 (s, 1 H), 6.34 (s, 1 H); ^{13}C NMR δ 14.2, 22.7, 23.5, 25.3, 26.2, 28.9, 30.2, 31.0, 31.7, 33.2, 36.1, 48.1, 55.8, 73.7, 103.6, 110.7, 116.3, 124.8, 139.0, 143.4, 155.8, 156.3.

Δ^9-THC ((−)-2). To a solution of (−)-**38** (40 mg, 0.116 mmol) in CH_2Cl_2 (5 mL) were added $ZnBr_2$ (52 mg, 0.23 mmol) and $MgSO_4$ (100 mg). The mixture was stirred at ambient temperature for 12 h and diluted with saturated $NaHCO_3$. The mixture was extracted with Et_2O twice. The combined organic layers were dried and concentrated to afford an oily residue, which was purified by chromatography (hexane/EtOAc) to furnish methyl ether of Δ^9-THC ((−)-**39**)[6h] (32 mg, 84% yield): $[\alpha]^{27}_D$ −112 (*c* 0.16, $CHCl_3$); IR (neat) 1615, 1575 cm^{-1}; ^1H NMR δ 0.89 (t, J = 7 Hz, 3 H), 1.08 (s, 3 H), 1.41 (s, 3 H), 1.67 (s, 3 H), 1.2−1.8 (m, 7 H), 1.84−1.98 (m, 2 H), 2.09−2.20 (m, 2 H), 2.50 (t, J = 8 Hz, 2 H), 3.17 (d, J = 11 Hz, 1 H), 3.84 (s, 3 H), 6.23 (br s, 1 H), 6.27 (br s, 1 H), 6.31 (br s, 1 H); ^{13}C NMR δ 14.2, 19.3, 22.7, 23.6, 25.3, 27.7, 31.0, 31.4, 31.8, 34.1, 36.2, 46.0, 55.3, 77.3, 103.0, 110.2, 110.4, 124.8, 133.4, 142.5, 154.3, 158.3.

To a solution of (−)-**39** (20 mg, 0.061 mmol) in DMF (5 mL) was added NaSEt (51 mg, 80% content, 0.485 mmol). After stirring at 120 °C for 8 h, the mixture was cooled to 0 °C and diluted with saturated $NaHCO_3$. The product was extracted with Et_2O twice. The combined organic layers were dried and concentrated to afford an oily residue, which was purified by chromatography (hexane/EtOAc) to furnish (−)-**2** (13 mg, 68% yield): $[\alpha]^{30}_D$ −145 (*c* 0.11, $CHCl_3$); lit.[6b] $[\alpha]^{28}_D$ −150 (*c* 1.0, $CHCl_3$). The IR, ^1H NMR, and ^{13}C NMR spectra were in good agreement with those reported in the literature[6i,23] for the enantiomer.

(3*R*,4*R*)-3-(3-Hydroxy-1-methoxynaphthalene-2-yl)-1-methyl-4-[(1-methyl-1-triethylsilyloxy)ethyl]-1-cyclohexene (41). A mixture of **31e** (135 mg, 0.297 mmol) and NaSEt (249 mg, 80% content, 2.37 mmol) in DMF (5 mL) was stirred at 120 °C for 12 h and diluted with saturated $NaHCO_3$. The product was extracted with Et_2O twice. The combined organic layers were dried and concentrated to afford an oily residue, which was purified by chromatography (hexane/EtOAc) to furnish **40** (80 mg, 62% yield): IR (neat) 3441, 1634, 1464 cm^{-1}; ^1H NMR (diagnostic signals) δ 1.78 (s, 3 H), 3.89 (s, 3 H), 4.11−4.22 (m, 1 H), 5.39 (br s, 1 H).

To an ice-cold solution of **40** (63 mg, 0.143 mmol) in THF (2 mL) was added TBAF (0.17 mL, 1.0 M in THF, 0.17 mmol). After 12 h at ambient temperature, the reaction was quenched with saturated $NaHCO_3$, and the product was extracted with EtOAc twice. The combined organic extracts were dried and concentrated to afford an oily residue, which was purified by chromatography (hexane/EtOAc) to furnish **41** (36 mg, 78% yield): IR (neat) 3419, 1736, 1631, 1598, 1577, 1504 cm^{-1}; ^1H NMR δ 1.12 (br s, 6 H), 1.52−1.70 (m, 2 H), 1.82 (br s, 3 H), 2.02−2.35 (m, 4 H), 3.95 (s, 3 H), 4.14−4.28 (m, 1 H), 5.51 (br s, 1 H), 6.70 (br s, 1 H), 6.77 (s, 1 H), 7.23−7.44 (m, 2 H), 7.64 (d, J = 8 Hz, 1 H), 8.08 (d, J = 8 Hz, 1 H). HRMS (CI) *m*/*z* calcd for $C_{21}H_{26}O_3$ (M^+) 326.1882, found 326.1873.

Naphthalene Analogue 42. To a solution of **41** (35 mg, 0.107 mmol) in CH_2Cl_2 (5 mL) was added $ZnBr_2$ (36 mg, 0.16 mmol) and $MgSO_4$ (150 mg). After 12 h at ambient temperature, saturated $NaHCO_3$ was added to the mixture and the product was extracted with Et_2O twice. The combined organic layers were dried and concentrated to afford an oily residue, which was purified by chromatography (hexane/EtOAc) to furnish **42** (30 mg, 91% yield): IR (neat) 1739, 1628, 1598, 1577, 1500, 1457, 1403 cm^{-1}; ^1H NMR δ 1.12 (s, 3 H), 1.56 (s, 3 H), 1.69 (s, 3 H), 0.9−2.3 (m, 5 H), 3.32 (d, J = 11 Hz, 1 H), 3.95 (s, 3 H), 6.23 (br s, 1 H), 6.72 (br s, 1 H), 7.23−7.42 (m, 2 H), 7.63 (d, J = 8 Hz, 1 H), 8.12 (d, J = 8 Hz, 1 H); ^{13}C NMR δ 19.2, 23.5, 25.2, 27.6, 31.4, 34.5, 46.1, 55.1, 77.6, 97.2, 110.5, 121.8, 121.9, 122.5, 124.9, 125.8, 126.1, 133.3, 133.6, 149.5, 156.9. HRMS (CI) *m*/*z* calcd for $C_{21}H_{24}O_2$ (M^+) 308.1776, found 308.1777.

Acknowledgment. We thank professor Y. Shoyama at Kyushu University for informing the guidelines to start this project. This work was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science, and Technology, Government of Japan. A.W. is grateful for the Sasakawa Scientific Research Grant from The Japan Science Society. We thank Mr. Yasumasa Tashiro of Nippon Chemiphar for measuring the high resolution mass spectra.

Supporting Information Available: Experimental procedures of closely related compounds and the ^1H NMR spectra of new compounds lacking elemental analyses. This material is available free of charge via the Internet at http://pubs.acs.org.

JO020457M