Stereoselective Construction of 22-Oxygenated Steroid Side Chains by Dimethylaluminum Chloride-Mediated Ene Reactions of Aldehydes

Todd A. Houston, Yoshio Tanaka, and Masato Koreeda*

Department of Chemistry, The University of Michigan, Ann Arbor, Michigan 48109-1055

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Dimethylaluminum chloride-mediated ene reactions of aldehydes with (*Z*)-3β-acetoxy-5,17(20)-pregnadiene (**3**) at low temperatures followed by acetylation of the resulting alcohols have been shown to produce stereoselectively 22-acetoxylated steroid derivatives in good to excellent yields. Interestingly, the stereochemical outcome of these ene reactions has been found to be dependent upon the size of the aldehyde employed; the less sterically demanding aldehydes such as 4-methylpentanal and cyclohexanecarboxaldehyde afford the (20α,22α)-22-acetoxy products (**4a**) stereoselectively, whereas the relatively congested aldehydes such as benzaldehyde and other aromatic aldehydes produce predominantly the (20α,22β)-22-acetates (**4b**). This novel stereochemical observation has been rationalized in terms of the relative stabilities of the two most plausible transition states where the difference in the relative bulk between the R group of the aldehyde RCHO and the Me_2AlCl coordinating to the aldehyde oxygen in an anti-fashion seems to be manifested in the stereochemical outcome at C-22 of the ene products.

Isolation of a variety of physiologically significant 22-oxygenated steroids from diverse sources has stimulated considerable interest in their stereocontrolled synthesis.[1] Several groups have placed focus on the simultaneous generation of two contiguous chiral centers at C-20 and -22 during the introduction of the side chain.[2] Research efforts from our laboratories have exploited the use of α-silyl radical cyclization[3] and [2,3]-Wittig rearrangement[4] as key stereodirecting processes at both C-20 and C-22, starting from the derivatives of a 16α-hydroxy-17-ethylidene steroid. The Lewis acid-mediated ene reaction[5] was employed in 1981 by Dauben[6] and by a team of chemists at Hoffmann-La Roche and Snider[7] as an efficient means of controlling stereochemistry at C-20 during the introduction of the steroid side chain with the use of (*Z*)-17(20)-ethylidene steroids (**1**). The use of this (*Z*)-olefin in the ene reactions allows for the stereocontrolled synthesis of the natural C-20 isomer due to the presence of the angular 18-methyl group, which precludes the reaction from taking place from the β face of the steroid nucleus. Moreover, when aldehydes other than formaldehyde are employed as enophiles, the potential for internal asymmetric induction at the two contiguous chiral centers, C-20 and 22, arises. In 1988, Nakai extended this dimethylaluminum chloride-promoted ene reaction method to methyl glyoxylate[8] and propargylic aldehydes.[9] In both cases, (20α,22α)-22-hydroxylated steroid[10] products were obtained with high stereoselectivity (see Scheme I). In conjunction with our interest in establishing convenient methods that might be suitable for access to both C-22 hydroxy isomers from a common steroid nucleus, the Me_2AlCl-mediated ene reaction of (*Z*)-17(20)-ethylidene steroids with various aldehydes was studied. In this paper, we describe an intriguing, hitherto unrecognized observation that the preferential formation of (22α)-**2a** or (22β)-22-hydroxy product **2b** is dependent on the type of aldehydes employed (see Scheme I) and provide mechanistic considerations in an attempt to elucidate the factors governing the stereochemical outcome.

The requisite (*Z*)-17(20)-ethylidene **3** was readily obtained from dehydroisoandrosterone in 84% overall yield by Wittig olefination[11] followed by acetylation. The Me_2AlCl-mediated ene reaction of this steroid turned out to be relatively sluggish when a solution of the steroid in methylene chloride was added to the Lewis acid/aldehyde solution in toluene at low temperatures, particularly in the reactions with aromatic aldehydes. Therefore, the reaction mixture was allowed to warm to rt and in all cases excess amounts of both the aldehyde and the Lewis acid were employed in an effort to drive the reaction to completion within several hours. Presumably, the acetate group present at C-3 interacts effectively with the Lewis acid, thus necessitating the use of excess Lewis acid. The crude reaction mixture obtained by quenching with

(1) Piatak, D. M.; Wicha, J. *Chem. Rev.* **1978**, *78*, 199. Turner, A. B. *Nat. Prod. Rep.* **1992**, *9*, 37.

(2) See, e.g., Mikami, K.; Kowamoto, K.; Nakai, T. *Tetrahedron Lett.* **1985**, *26*, 5799. *Ibid.* **1986**, *27*, 4899.

(3) Koreeda, M.; George, I. A. *J. Am. Chem. Soc.* **1986**, *108*, 8098. *Chem. Lett.* **1990**, 83.

(4) Koreeda, M.; Ricca, D. J. *J. Org. Chem.* **1986**, *51*, 4090.

(5) (a) Snider, B. B. *Acc. Chem. Res.* **1980**, *13*, 426. (b) Desimoni, G.; Tacconi, G.; Barco, A.; Pollini, G. P. *Natural Products Synthesis through Pericyclic Reactions*; ACS Monograph 180, Americal Chemical Society: Washington, D.C., 1983; Chapt. 8. (c) Snider, B. B. In *Comprehensive Organic Synthesis*; Paquette, L. A., Ed.; Pergamon: London, 1991; Vol. 5, 1.1. (d) Mikami, K.; Shimizu, M. *Chem. Rev.* **1992**, *92*, 1021.

(6) Dauben, W. G.; Brookhart, T. *J. Am. Chem. Soc.* **1981**, *103*, 237. *J. Org. Chem.* **1982**, *47*, 3921.

(7) Batcho, A. D.; Berger, D. E.; Uskokovic, M. R.; Snider, B. B. *J. Am. Chem. Soc.* **1981**, *103*, 1293. See also: Batcho, A. D.; Berger, D. E.; Davoust, S. G.; Wavkulich, P. M.; Uskokovic, M. R. *Helv. Chim. Acta* **1981**, *64*, 1682.

(8) Mikami, K.; Loh, T.-P.; Nakai, T. *Tetrahedron Lett.* **1988**, *29*, 6305.

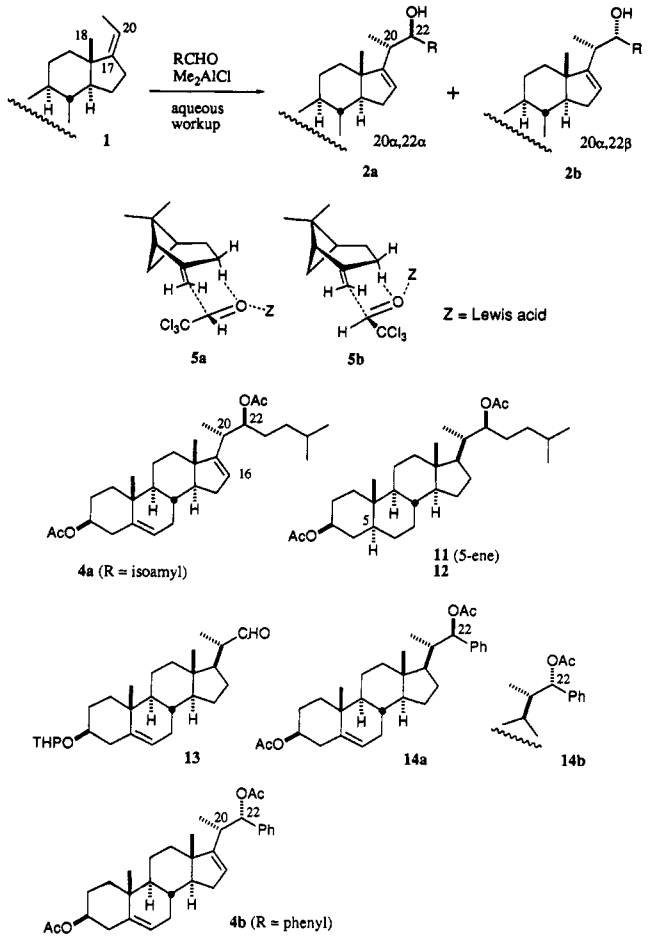
(9) Mikami, K.; Loh, T.-P.; Nakai, T. *J. Chem. Soc., Chem. Commun.* **1988**, 1430.

(10) The use of the nomenclature based on the sequence rules of Cahn, Ingold, and Prelog for the description of the C-22 stereochemistry of the ene products from **3** results in different designations for products of the same stereochemistry depending upon the R group in **2a**/**2b**, e.g., 22*R* or 22*S* when R is isoamyl or phenyl in **2a**, respectively. Therefore, for the sake of avoiding confusion in the mechanistic consideration involving the C-22 chiral center, the Fieser–Plattner convention involving the α or β designation is employed in this paper for the description of the stereochemistry at C-20/22. For the rule of this α,β-designation of the steroid side chain stereochemistry, see ref 1a.

(11) Drefahl, G.; Ponsold, K.; Schick, H. *Helv. Chim. Acta* **1965**, *98*, 604.

0022-3263/93/1958-4287$04.00/0

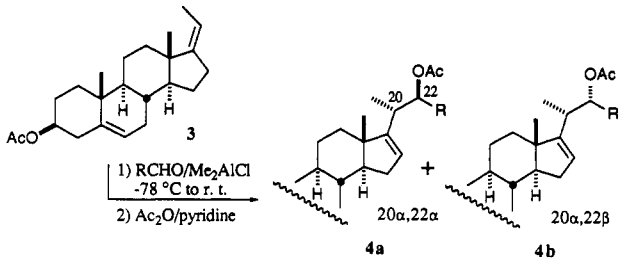
Scheme I



MeOH/water at −78 °C followed by acetylation was purified as their inseparable mixture of 22-acetate epimers.

The stereochemical outcome of the Me_2AlCl-mediated ene reactions of (*Z*)-17(20)-ethylidene **3** with various aldehydes, summarized in Table I, seems to indicate its unexpected dependence on the type of aldehyde employed. Thus, while the use of aliphatic aldehydes resulted in the preferential formation of the 22α products (entries 1 and 7; see also entries 11 and 12), that of aromatic aldehydes favored the generation of the 22β-isomers (entries 2 and 4–6). The formation of the 20α,22α-products **4a** with aliphatic aldehydes seems in good agreement with the stereoselectivities observed by Snider[13] in the Me_2AlCl-catalyzed ene reactions of similar trisubstituted acyclic olefins. The reaction may proceed through the transition state **TS-α** (Figure 1) as it has been shown that most Me_2AlCl-mediated ene reactions occur through such a cyclic transition state.[5c,d,14] It should also be noted that although coordination of the aluminum reagent on the aldehyde oxygen in an anti-fashion to the alkyl group of the aldehyde has not bee rigorously proven in the present reaction, such anti-mode coordination seems reasonable on the basis of recent reports on the anti-coordination of other Lewis acids to aldehyde oxygens.[15] An alternate transition state, **TS-β**, that leads to the formation of the minor epimer places the tetravalent coordinated aluminum species in a more sterically cumbersome position, directly underneath the steroid D-ring. In 1984, Gill[16] showed that Lewis acids

Table I. Me_2AlCl-Mediated Ene Reactions of Pregnadiene 3 with Various Aldehydes



entry[a]	R	% yield (4a + 4b)	4a/4b[b]	reference
1	isoamyl	91	12:1	this work
2	phenyl	92	1:9	this work
3	phenyl (rt)	80	4:3	this work
4	*o*-tolyl	60	1:>25	this work
5	*o*-nitrophenyl	>53	1:1.5	this work
6	2-furyl	56	1:19	this work
7	cyclohexyl	60	14:1	this work
8	*tert*-butyl	no ene adduct		this work
9[c]	C≡CCH$_3$	90	9:1	ref 9
10[c]	C≡CSi(CH$_3$)$_3$	100	**4a** only	ref 9
11[c]	COOMe	100	**4a** only	ref 8
12[c]	CH_2Cl	73	**4a** only	ref 12

[a] All ene reactions were run at −78 °C and the reaction mixtures were warmed slowly to rt (see Experimental Section) except for the reaction described in entry 3. [b] Ratios were determined by integration of the C-22 proton peaks in the ^1H NMR spectra of the ene adducts **4a**/**4b** in $CDCl_3$. [c] (*Z*)-6β-Methoxy-3α,5α-cyclo-17(20)-pregnene was employed for the ene reactions in place of **3**.

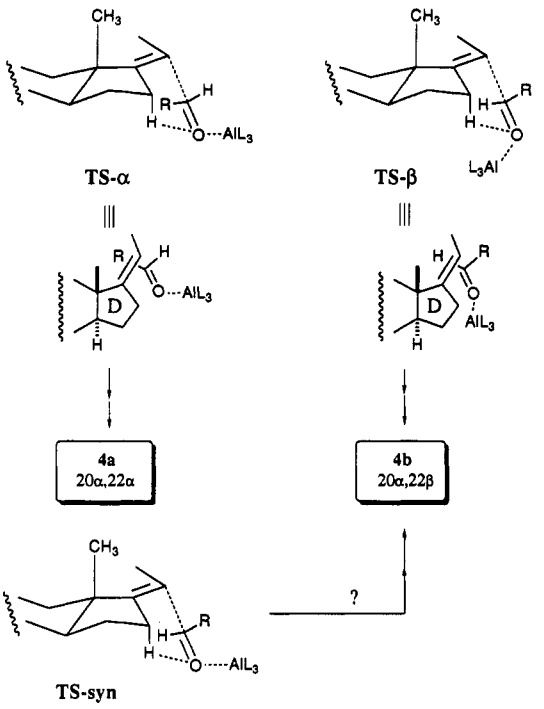


Figure 1. Transition states for the Me_2AlCl-mediated ene reactions of **3**.

(12) Mikami, K.; Loh, T.-P.; Nakai, T. *J. Chem. Soc., Chem. Commun.* **1991**, 77.

(13) Cartaya-Marin, C.; Jackson, A. C.; Snider, B. B. *J. Org. Chem.* **1984**, *49*, 2443.

(14) Marshall, J. A.; Andersen, M. W. *J. Org. Chem.* **1992**, *57*, 5851. For the theoretical calculations on the transition states of thermal ene reactions, see: Loncharich, R. J.; Houk, K. N. *J. Am. Chem. Soc.* **1987**, *109*, 6947.

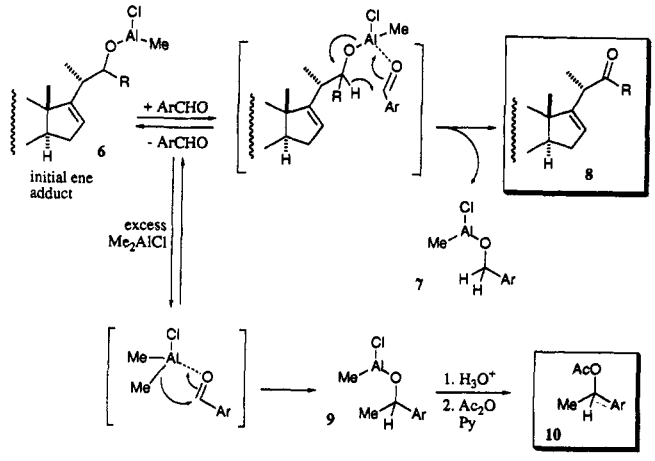
(15) (a) Reetz, M. T.; Hüllmann, M.; Massa, W.; Berger, S.; Rademacher, P.; Heymanns, P. *J. Am. Chem. Soc.* **1986**, *108*, 2405. (b) Corey, E. J.; Loh, T.-P.; Sarshar, S.; Azimioara, M. *Tetrahedron Lett.* **1992**, *33*, 6945. (c) For an excellent review on the structures of Lewis acid complexes of carbonyls, see: Shambayati, S.; Crowe, W. E.; Schreiber, S. L. *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 256.

coordinated to chloral prefer an exo disposition (see **5a**) in the transition state of the Lewis acid-mediated ene reactions with β-pinene. Furthermore, it was observed that this preference of the transition state **5a** over **5b** increases proportionally with increasing size of the Lewis acid.[17] However, an intriguing alternative possibility does exist: the involvement of the complex of the aluminium reagent "syn" to the aldehyde alkyl group in the transition state might account for the formation of the minor epimers (see **TS-syn**). In this context, it is of considerable interest to note that the results of the recent *ab initio* MO calculations of the acetaldehyde–boron trifluoride complex predict that the complex exists as an 88:12 mixture of the anti and syn forms, respectively.[18] Interestingly, this ratio is quite close to that of the isomeric product distribution observed in entries 1 and 7.

In marked contrast to the above-mentioned aliphatic aldehydes, the use of benzaldehyde and other aromatic aldehydes in the ene reaction with **3** resulted in the predominant formation of the opposite C-22β-epimer (see entries 2, 4, and 6, Table I). It appears conceivable that the gauche interaction between the aryl and the C-20 methyl groups or the quasiaxial orientation of the bulk aryl group in **TS-α** must destablize this transition state to such a degree that **TS-β** now becomes the preferred pathway in spite of the potential steric congestion encountered by the aluminum complex. While syn-complexation of the aluminum reagent to the aldehyde might allow the formation of the 22β-isomer through a transition state such as **TS-syn**, it should be noted that the benzaldehyde–boron trifluoride complex is predicted to exist exclusively in an anti disposition,[18] and a syn complex should be even less likely for the larger aluminum species. This propensity for the formation of the 22β-epimer was even more pronounced for *o*-tolualdehyde as only the 20α,-22β-diastereomer (entry 4) was obtained. Interestingly, replacement of the methyl group on the aromatic ring with a nitro group led to highly increased reactivity in the ene reaction (the reaction was complete in 2.5 h, at temperatures below −60 °C) and decreased stereoselectivity (see entry 5). When the reaction with benzaldehyde was carried out at room temperature, virtually no stereoselectivity for the formation of ene products was observed (see entry 3), possibly indicating that the 22β-isomer is the kinetic product. Thus, it may follow that the less reactive aromatic aldehyde, *o*-tolualdehyde, would have greater kinetic selectivity than the more reactive *o*-nitrobenzaldehyde.

For each of these ene reactions it proved necessary to maintain at least a 2-fold excess of the Lewis acid relative to the aldehyde. When the aldehyde is used in an equimolar or greater ratio relative to the Me_2AlCl, the initial ene adduct is prone to oxidation to the ketone, presumably through an Oppenauer-type oxidation[19] (Scheme II). This oxidation reaction was observed to be a major process in certain cases. For example, the ene

Scheme II



reaction of **3** with 6 equiv of benzaldehyde in the presence of 3 equiv of Me_2AlCl at rt for 6 h, provided the keto product **8** in 65% yield. A consequence of increasing the amount of Me_2AlCl is that the rate of methyl addition from the aluminum reagent to the aldehyde is enhanced (see **6** to **9** in Scheme II). In the case of *o*-nitrobenzaldehyde, this methyl addition reaction is quite prevalent as the acylated byproduct **10** was found to comprise 30–40% of the crude reaction product mixture. Accordingly, the stoichiometry of the reactants in the ene reactions of **3** was chosen to balance these two aberrant reaction pathways. Additionally, the use of the 2:1 Me_2AlCl/aldehyde ratio should disfavor the formation of the initial ene-adduct·aldehyde complex (see Scheme II) as virtually all aldehyde molecules should be complexed with the Lewis acid. Therefore, the ene reaction conditions employed herein are likely to further suppress the product formation involving reversible Oppenauer oxidation-/Meerwein–Ponndorf reduction type processes.

The stereochemical results described above may alternatively be viewed as being a consequence of the use of conjugated versus nonconjugated aldehydes.[20] However, the observation by Nakai[9] that the use of conjugated, propargylic aldehydes results in the formation of 22α-adducts (see entries 9 and 10 in Table I) does not appear to favor this notion. These results with propargylic aldehydes seem to be in accordance with the interpretation that the difference in relative steric bulk between the aldehyde substituent and the coordinated aluminum metal groups dictates the stereochemical outcome of the ene adducts. Thus, the smaller aldehydes are likely to prefer the transition state (see **TS-α**) where the aldehyde chain rather than the bulkier aluminum catalyst lies beneath the steroid nucleus, whereas the opposite is the case for the bulkier aromatic aldehydes (Figure 1). While the results of bulky, aliphatic aldehydes such as pivalaldehyde could have been more informative in evaluation of the interpretation based on the steric sizes, the Me_2AlCl-catalyzed reaction of this aldehyde with **3** did not produce any ene product (entry 8, Table I).

The stereochemical assignments of the ene reaction products were made through chemical correlation of the two representative ene adducts (i.e., isoamyl and phenyl

(16) Benner, J. P.; Gill, G. Bryon; Parrott, S. J.; Wallace, B.; Begley, M. J. *J. Chem. Soc., Perkin Trans. 1* **1984**, 315.

(17) It should be noted in this β-pinene case, the steric bulk of trichloromethyl group does not appear to play a significant role in the stereochemical outcome of the Lewis acid-catalyzed ene reaction due to the absence of a methyl group at the terminal olefinic carbon, thus negating a potentially significant gauche interaction between the trichloromethyl and methyl groups.

(18) (a) Gung, B. W. *Tetrahedron Lett.* **1991**, *32*, 2867. (b) Gung, B. W.; Wolf, M. A. *J. Org. Chem.* **1992**, *57*, 1370.

(19) (a) Snider, B. B.; Goldman, B. E. *Tetrahedron* **1986**, *42*, 2951. (b) Majewski, M.; Bantle, G. W. *Synth. Commun.* **1990**, *20*, 2549.

(20) α,β-Unsaturated aldehydes and ketones could not be used for the present study since they are known to undergo a Michael addition-type reaction by an olefin, instead of the ene reaction onto the carbonyl carbon, in the presence of Me_2AlCl. See: Snider, B. B.; Deutsch, E. A. *J. Org. Chem.* **1982**, *47*, 745.

adducts, entries 1 and 2, Table I, respectively), with either known compounds or the stereoisomer prepared by a well-documented method. The diacetate derivative of the ene product **4a** (R = isoamyl) was subjected to catalytic hydrogenation with either 1 or 2 equiv of hydrogen to yield the known (22*R*)-3β,22-diacetoxy-5-cholestene (**11**)[21] and -5α-cholestane (**12**).[22] Melting point, optical rotation, as well as spectroscopic data for these products were in complete agreement with those of their respective authentic compounds. For confirmation of the ene adduct of benzaldehyde (entry 2), a 2.5:1 mixture of C-22 epimers **14a/14b** was obtained quantitatively by the addition of phenylmagnesium bromide to aldehyde **13** followed by mild acid treatment and acetylation. The stereochemistry of the major epimer **14a** was assigned by comparison with the results observed for various alkyllithium or Grignard additions of bulky nucleophiles to this aldehyde where the preferential formation of the Cram product, i.e., the 22α-epimer, is well-precedented.[23,24] Catalytic hydrogenation of the ene adduct **4b** (R = phenyl; entry 2, Table I) provided a compound whose spectroscopic properties are identical with those of **14b**. The stereochemical assignments of the other ene products were made through comparison of the magnitude of the vicinal coupling constants between the two hydrogens at C-20 and C-22 with those of **4a** (R = isoamyl) and **4b** (R = phenyl). Thus, it has been empirically deduced in this study that the vicinal coupling constants ($^3J_{20,22}$) of the (20α,22β)-22-acetoxy-16-ene steroid compounds are larger than those of their corresponding 22α-epimers.[25] In cases where the $^3J_{20,22}$ values were not obtainable on the minor 22-epimers due to their low concentrations in the respective mixture, the coupling constants of the major epimers were compared with that of the acetates of either the isoamyl when R = cyclohexyl or phenyl ene products when R = *o*-tolyl, *o*-nitrophenyl, or 2-furyl.

The dichotomous behavior of various aldehydes described above seems to have little precedent in ene reaction chemistry. This unusual observation may be rationalized through analysis of the relative stabilities of the two most plausible transition states where the difference in the relative bulk between the aldehyde group and the Me_2AlCl coordinating to the aldehyde oxygen in an anti-fashion seems to control the selectivity. While the phenyl and cyclohexyl cases might be expected to give similar results based on this argument, it should be noted that the A-value of a cyclohexyl substituent ($-\Delta G$ = 2.15 kcal/mol at 30 °C) is close to that of an ethyl substituent (1.75 kcal/mol) and is considerably smaller than that of a phenyl group (3.0 kcal/mol).[26] The use of these A-values in this context may be justified since the two transition states, **TS-α** and **TS-β**, are six-membered chair-like conformations where R groups may be viewed as being axially and equatorially oriented, respectively (see Figure 1). The above-mentioned application of ene reaction should prove useful as it provides highly selective entries into both C-22 hydroxy isomers from a single steroidal olefin precursor.[27] Selective hydrogenation of the C16, 17 double bond secures three contiguous chiral centers C-17, 20, and 22. Application of this methodology to the synthesis of natural steroid side chains is underway.

Experimental Section

(*Z*)-3β-Acetoxy-5,17(20)-pregnadiene (3). To a suspension of (ethyl)triphenylphosphonium bromide (6.51 g, 17.5 mmol) in 50 mL of dry THF was added a solution of potassium *tert*-butoxide (2.01 g, 17.8 mmol) in dry THF (20 mL) at room temperature. After 30 min, a solution of dehydroisoandrosterone (1.00 g, 3.47 mmol; purchased from United States Biochemical Corp., Cleveland, OH) in dry THF (25 mL) was added. The mixture was refluxed for 3.5 h and the reaction was quenched with 50 mL of saturated aqueous NH_4Cl. The aqueous layer was separated and extracted with EtOAc (3 × 30 mL). The combined organic layers were washed successively with saturated aqueous NH_4Cl, deionized water, and saturated aqueous NaCl and then dried (Na_2SO_4). Removal of solvent by rotary evaporation gave a white solid which was passed through a short SiO_2 column to furnish 1.02 g of crude (*Z*)-3β-hydroxy-5,17(20)-pregnadiene which was subjected to acylation without further purification. A mixture of (*Z*)-3β-hydroxy-5,17(20)-pregnadiene (1.02 g), Ac_2O (2 mL), and pyridine (2 mL) in CH_2Cl_2 (3 mL) was stirred at room temperature for 12 h. The reaction was quenched with 5 mL of ice–water and the resulting mixture was extracted with Et_2O (3 × 5 mL). The combined organic layers were washed successively with 1 M aqueous HCl, saturated aqueous $NaHCO_3$, and saturated aqueous NaCl and were dried (Na_2SO_4). Removal of solvent by rotary evaporation and purification of the resulting crude acetate by silica gel flash column chromatography using 10% (v/v) EtOAc/hexanes as the eluent afforded 1.0 g of **3** as a white solid (84%): mp 96–98 °C (hexanes); $[\alpha]^{23}_D$ –65° (*c* 2.52, $CHCl_3$); ^{1}H NMR (360 MHz, $CDCl_3$) δ 0.87 (s, 3 H, 18-H), 1.01 (s, 3 H, 19-H), 1.64 (apparent dt, 3 H, *J* = 7.2, 2.0 Hz, 21-H), 2.01 (s, 3 H, OAc), 4.55–4.65 (m, 1 H, 3-H), 5.13 (apparent qt, 1 H, *J* = 7.2, 2.2 Hz, 20-H), 5.36 (br d, 1 H, *J* = 5.0 Hz, 6-H); ^{13}C-NMR (90 MHz, $CDCl_3$) δ 13.09 (q), 16.71 (q), 19.31 (q), 21.28 (t), 21.35 (q), 24.57 (t), 27.92 (t), 31.56 (d), 31.62 (t), 31.84 (t), 36.80 (s), 37.14 (t), 38.28 (t), 44.15 (s), 50.34 (d), 56.69 (d), 73.99 (d), 113.55 (d), 122.45 (d), 139.88 (s), 150.14 (s), 170.20 (s); IR (KBr) 2942, 1731, 1374, 1261, 1246, 1041 cm^{-1}. Anal. Calcd for $C_{23}H_{34}O_2$: C, 80.65; H, 10.01. Found: C, 80.43; H, 10.15.

Ene Adduct of 3 and 4-Methylpentanal (entry 1, Table I). To a solution of 4-methylpentanal (135 mg, 1.35 mmol) in CH_2Cl_2 (5 mL) was added 25% Me_2AlCl in toluene (1.0 mL, 2.3 mmol) at –78 °C. After 5 min a solution of pregnadiene **3** (150 mg, 0.438 mmol) in CH_2Cl_2 (1 mL) was added. The resulting mixture was warmed from –78 °C to room temperature over 10 h at which point the reaction was quenched with 10 mL of MeOH/water (1:1) at –78 °C. The mixture was separated and the aqueous layer was extracted with ether (3 × 10 mL). The organic layers were combined and washed successively with 1% aqueous HCl, saturated aqueous $NaHCO_3$, saturated aqueous NaCl and then dried over anhydrous Na_2SO_4. Removal of solvent by rotary evaporation gave the crude alcohol as a viscous oil.

The crude alcohol thus obtained was dissolved in a mixture of pyridine (1 mL) and $CHCl_3$ (1 mL) and was treated with acetic

(21) Poyster, P. J.; Ourisson, G. *J. Chem. Soc., Perkin Trans. 1* **1974**, 2061.

(22) Mori, H.; Shibata, K.; Tsuneda, K.; Sawai, M.; Tsuda, K. *Chem. Pharm. Bull.* **1968**, *16*, 1407.

(23) See, e.g., Tsubuki, M.; Kanai, K.; Keino, K.; Kakinuma, N.; Honda, T. *J. Org. Chem.* **1992**, *57*, 2930. See also: Bartlett, P. A. *Tetrahedron* **1980**, *36*, 2.

(24) It may be argued that the use of aqueous acidic conditions (see Experimental Section) for deprotection of the THP ether group in the preparation of **14a** could potentially alter the ratio of the 22-epimers of initially produced benzylic alcohols. However, the ^{1}H NMR spectrum of the acetates of the crude phenyl Grignard adducts, which were not subjected to the above aqueous acidic treatment, exhibited virtually identical 22-H peak patterns with a similar epimeric ratio to that of **14a**. Therefore, the C-22 epimer ratio determined for **14a** should closely reflect that of the initially produced phenyl Grignard adducts of **13**.

(25) The $^3J_{20,22}$ values observed are as follows: R = isoamyl: 8.3 Hz (**4a**) and 9.5 Hz (**4b**); R = phenyl: 8.3 Hz (**4a**) and 9.8 Hz (**4b**); R = 2-furyl: 12.5 Hz (**4b**); R = *o*-tolyl: 10.3 Hz (**4b**); R = *o*-nitrophenyl: 5.3 Hz (**4a**) and 8.8 Hz (**4b**); R = cyclohexyl: 8.4 Hz (**4a**).

(26) Gordon, A. J.; Ford, R. A. *The Chemist's Companion-A Handbook of Practical Data, Techniques, and References*; John Wiley & Sons: New York, 1972; pp 156–157. See also: Hirsch, J. A. In *Topics in Stereochemistry*; Allinger, N. L.; Eliel, E. L., Eds.; John Wiley & Sons: New York, 1967; Vol. 1, pp 199–222.

(27) For other reported divergent approaches toward the synthesis of 22-hydroxylated steroids, see refs 2, 5d, 8, 9, and 12 and Yamamoto, Y.; Nishii, S.; Yamada, J. *J. Am. Chem. Soc.* **1986**, *108*, 7116.

anhydride (1 mL) at room temperature. The solution was stirred at room temperature for 12 h and then diluted with ether. The mixture was washed successively with 1% aqueous HCl, saturated aqueous $NaHCO_3$, saturated aqueous NaCl and then dried over anhydrous Na_2SO_4. The organic layer was then concentrated and purified by silica gel flash chromatography on SiO_2 with 10% EtOAc/hexanes as the eluent to furnish 194 mg of a 12:1 mixture of **4a/4b** (R = isoamyl) (91% yield for two steps) as a white solid: mp 120–22 °C (MeOH/acetone). *This two step procedure represents our standard protocol for the isolation of all ene reaction products.* For **4a** (R = isoamyl): ^{1}H NMR (360 MHz, $CDCl_3$) δ 0.81 (s, 3 H, 18-H), 0.84 (d, 3 H, J = 6.6 Hz) and 0.85 (d, 3 H, J = 6.6 Hz) (26, 27-H), 0.99 (d, 3H, J = 6.8 Hz, 21-H), 1.06 (s, 3 H, 19-H), 2.04 (s, 3 H, OAc), 2.07 (s, 3 H, OAc), 4.52–4.74 (m, 1 H, 3-H), 5.00 (ddd, 1 H, J = 8.3, 3.7, 3.7 Hz, 22-H), 5.40 (br d, 1 H, J = 4.9 Hz, 6-H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 16.27, 17.87, 19.26, 20.78, 21.22, 21.44, 22.42, 22.72, 27.85, 27.96, 30.59, 31.39, 31.66, 34.69, 35.00, 35.06, 36.48, 36.92, 37.04, 38.24, 47.28, 50.77, 57.39, 74.02, 77.18, 122.63, 123.40, 140.15, 157.43, 170.66, 171.12; IR ($CHCl_3$) 1735 cm^{-1}; MS (CI-CH_4 23 eV) m/z 485 (2.5, $[M + 1]^+$), 425 (100, $[M + 1 - 60]^+$). Anal. Calcd for $C_{31}H_{48}O_4$: C, 76.81; H, 9.98. Found: C, 76.79; H, 10.21.

Ene Adduct of 3 and Benzaldehyde (entry 2, Table I). To a solution of benzaldehyde (300 mg, 2.83 mmol) in CH_2Cl_2 (2 mL) was added 25% Me_2AlCl in toluene (2.0 mL, 4.6 mmol) at −78 °C. After 5 min a solution of pregnadiene **3** (200 mg, 0.585 mmol) in CH_2Cl_2 (5 mL) was added. The resulting mixture was warmed from −78 °C to room temperature over 18 h. The reaction was quenched at −78 °C with 10 mL of MeOH/water (1:1). Standard workup, followed by acetylation and flash chromatography using 10% EtOAc/hexanes as the eluent (vide supra) furnished 263 mg (92% from **3**) of a 1:9 mixture of **4a/4b** (R = phenyl) as a white solid: mp 165–168 °C (MeOH). For **4b** (R = phenyl): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.77 (d, 3 H, J = 7.1 Hz, 21-H), 0.80 (s, 3 H, 18-H), 1.07 (s, 3 H, 19-H), 1.96 (s, 3 H, OAc), 2.04 (s, 3 H, OAc), 2.33 (apparent d, 2 H, J = 7.1 Hz), 2.5–2.65 (m, 1 H), 4.5–4.7 (m, 1 H, 3-H), 5.38 (br d, 1 H, J = 5.0 Hz, 6-H), 5.47 (br s, 1 H, 16-H), 5.75 (d, 1 H, J = 9.8 Hz, 22-H), 7.27–7.47 (m, 5 H); ^{13}C-NMR (90 MHz, $CDCl_3$) δ 15.58 (q), 19.24 (q), 19.37 (q), 20.73 (t), 21.18 (q), 21.44 (q), 27.78 (t), 30.59 (d), 31.34 (t), 31.61 (t), 34.66 (t), 36.85 (s), 36.95 (t), 37.64 (d), 38.16 (t), 47.28 (s), 50.71 (d), 57.11 (d), 73.93 (d), 78.85 (d), 122.24 (d), 122.52 (d), 127.45 (d), 127.95 (d), 128.25 (d), 139.79 (s), 139.93 (s), 156.81 (s), 170.04 (s), 170.55 (s); IR ($CHCl_3$) 2935, 1734, 1373, 1243, 1031 cm^{-1}. MS (CI-NH_3, 23 eV) m/z 508 (68, $[M + 18]^+$), 448 (47, $[M + 18 - OAc]^+$), 431 (19), 182 (100). Anal. Calcd for $C_{32}H_{42}O_4$: C, 78.33; H, 8.63. Found: C, 78.30; H, 8.65.

Ene Adduct of 3 and *o*-Tolualdehyde (entry 4, Table I). To a solution of *o*-tolualdehyde (100 mg, 0.833 mmol) in CH_2Cl_2 (2 mL) was added 25% Me_2AlCl in toluene (1.0 mL, 2.30 mmol) at −78 °C. After 5 min a solution of pregnadiene **3** (100 mg, 0.292 mmol) in CH_2Cl_2 (3 mL) was added. The resulting mixture was warmed from −78 °C to room temperature over 10 h at which time the reaction was quenched with 10 mL of MeOH/water (1:1) at −78 °C. Standard workup followed by acetylation and flash chromatography using 10% EtOAc/hexanes as the eluent afforded 89 mg (60% from **3**) of **4b** (R = *o*-tolyl) as a white solid observed to be a single diastereomer by ^{1}H NMR analysis: mp 194–196 °C (MeOH/acetone); ^{1}H NMR (360 MHz, $CDCl_3$) δ 0.78 (d, 3 H, J = 7.3 Hz, 21-H), 0.80 (s, 3 H, 18-H), 1.07 (s, 3 H, 19-H), 1.93 (s, 3 H, OAc), 2.04 (s, 3 H, OAc), 2.49 (s, 3 H, $ArCH_3$), 4.55–4.65 (m, 1 H, 3-H), 5.40 (br d, 1 H, J = 5.0 Hz, 6-H), 5.53 (br s, 1 H, 16-H), 6.04 (d, 1 H, J = 10.3 Hz, 22-H), 7.11–7.35 (m, 4 H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 15.60 (q), 18.81 (q), 19.26 (q), 19.60 (q), 20.82 (t), 21.06 (q), 21.40 (q), 27.86 (t), 30.73 (d), 31.40 (t), 31.69 (t), 34.84 (t), 36.94 (s), 37.05 (t), 38.25 (t), 38.28 (d), 47.39 (s), 50.86 (d), 57.25 (d), 74.00 (d), 75.21 (d), 122.23 (d), 122.58 (d), 126.19 (d), 126.75 (d), 127.66 (d), 130.33 (d), 136.41 (s), 138.77 (s), 140.11 (s), 157.29 (s), 170.06 (s), 170.53 (s); IR (KBr) 2970, 2939, 1733, 1370, 1250, 1235, 1035, 1021 cm^{-1}; MS (CI-NH_3, 23 eV) m/z 522 (11.2, $[M + 18]^+$), 478 (2.8, $[M + 18 - 42]^+$), 462 (15, $[M + 18 - 60]^+$), 445 (57), 391 (100), 385 (46), 279 (61). Anal. Calcd for $C_{33}H_{44}O_4$: C, 78.53; H, 8.79. Found: C, 78.49; H, 8.81.

Ene Adduct of 3 and *o*-Nitrobenzaldehyde (entry 5, Table I). To a solution of pregnadiene **3** (118 mg, 0.345 mmol) and *o*-nitrobenzaldehyde (205 mg, 1.36 mmol) in CH_2Cl_2 (3 mL) was added Me_2AlCl (2.50 mL, 2.50 mmol) at −78 °C. The resulting solution was warmed from −78 to −60 °C over 2.5 h at which time the reaction was quenched by the addition of 10 mL of MeOH/water (1:1) and the resulting mixture was extracted with CH_2Cl_2 (3 × 10 mL). Combined organic layers were dried (Na_2SO_4) and concentrated. Acetylation of the crude reaction mixture (vide supra) gave an approximately 1:1 mixture of acetylated ene adducts [2:3 **4a/4b** (R = *m*-nitrophenyl)] and 2-(1-acetoxyethyl)-nitrobenzene (**10**). Fractional crystallization of the crude product mixture from MeOH provided 98 mg (53% yield from **3**) of a 1:6 mixture of **4a/4b** (R = o-nitrophenyl) as a faint yellow solid. Further recrystallization of this mixture from MeOH furnished the pure 22β-epimer **4b** (R = *o*-nitrophenyl): mp 200–5 °C dec (MeOH); ^{1}H NMR (360 MHz, $CDCl_3$) δ 0.64 (s, 3 H, 18-H), 0.96 (d, 3 H, J = 7.3 Hz, 21-H), 1.05 (s, 3 H, 19-H), 1.97 (s, 3 H, OAc), 2.04 (s, 3 H, OAc), 2.7–2.8 (m, 1 H), 4.55–4.75 (m, 1 H, 3-H), 5.40 (m, 1 H, J = 5.0 Hz, 6-H), 5.64 (br s, 1 H, 16-H), 6.42 (d, 1 H, J = 8.8 Hz, 22-H), 7.42 (ddd, 1 H, J = 8.2, 6.4, 2.3 Hz), 7.54–7.62 (m, 2 H), 7.87 (d, 1 H, J = 8.5 Hz); ^{13}C NMR (90 MHz, $CDCl_3$) δ 15.40 (q), 19.16 (q), 19.22 (q), 20.71 (q), 20.82 (t), 21.42 (q), 27.79 (t), 30.61 (d), 31.35 (t), 31.60 (t), 34.66 (t), 36.86 (t), 36.96 (s), 37.81 (d), 38.17 (t), 47.26 (s), 50.69 (d), 57.13 (d), 73.66 (d), 73.93 (d), 122.47 (d), 123.55 (d), 124.26 (d), 128.50 (d), 128.59 (d), 132.75 (d), 135.37 (s), 139.98 (s), 149.39 (s), 156.05 (s), 169.87 (s), 170.53 (s); IR (KBr) 1732, 1530, 1373, 1240, 1031 cm^{-1}. HRMS (CI-NH_3, 23 eV) calcd for $C_{32}H_{41}NO_6 \cdot NH_4$ m/z 553.3278, found 553.3255. Microanalysis was not performed on this ene adduct due to its instability as indicated by the rapid yellow colorization upon standing at rt. **2-(1-Acetoxyethyl)nitrobenzene** (**10**: Ar = *o*-nitrophenyl): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.64 (d, 3 H, J = 6.5 Hz), 2.07 (s, 3 H, OAc), 6.32 (q, 1 H, J = 6.5 Hz), 7.4–7.5 (m, 1 H), 7.6–7.7 (m, 2 H), 7.94 (apparent d, 1 H, J = 7.7 Hz).

Ene Adduct of 3 and 2-Furfural (entry 6, Table I). To a solution of 2-furfural (120 mg, 1.25 mmol) and 2,6-di-*tert*-butyl-4-methylphenol (25 mg, 0.114 mmol) in CH_2Cl_2 (2 mL) was added 25% Me_2AlCl in toluene (1.0 mL, 2.3 mmol) at −78 °C. After 5 min a solution of pregnadiene **3** (100 mg, 0.292 mmol) in CH_2Cl_2 (5 mL) was added. The resulting mixture was warmed from −78 °C to rt over 15 h at which time the reaction was quenched by the addition of 10 mL of MeOH/water (1:1) at −78 °C. Standard workup followed by acylation and flash chromatography with 20% EtOAc/hexanes as the eluent (vide supra) afforded 79 mg (56%) of a 1:19 mixture of **4a/4b** (R = 2-furyl) as a pale yellow amorphous solid: ^{1}H NMR (360 MHz, $CDCl_3$) δ 0.84 (d, 3 H, J = 7.1 Hz, 21-H), 0.91 (s, 3 H, 18-H), 0.97 (s, 3 H, 19-H), 2.03 (s, 3 H, OAc), 2.05 (s, 3 H, OAc), 4.55–4.65 (m, 1 H, 3-H), 4.68 (d, 1 H, J = 12.5 Hz, 22-H), 5.35–5.45 (m, 2 H); IR (KBr) 1740, 1728 cm^{-1}. MS (CI-CH_4, 23 eV) m/z: 437 (5, $[M - 43]^+$), 421 (5, $[M - 59]^+$), 377 (9), 361 (4), 341 (2), 313 (20), 281 (5), 253 (5), 123 (100). Anal. Calcd for $C_{30}H_{40}O_5$: C, 74.97; H, 8.39. Found: C, 74.60; H, 8.44.

Ene Adduct of 3 and Cyclohexanecarboxaldehyde (entry 7, Table I). To a solution of cyclohexanecarboxaldehyde (0.14 mL, 1.16 mmol) and pregnadiene **3** (95 mg, 0.277 mmol) in CH_2Cl_2 (5 mL) was added 1 M Me_2AlCl in hexanes (1.20 mL, 1.20 mmol) at −78 °C. The resulting mixture was warmed from −78 °C to room temperature over 12 h. Stirring was continued at this temperature for 4 h at which time the reaction mixture was cooled to 0 °C and quenched by the addition of 10 mL of MeOH/water (1:1). Standard workup followed by acetylation and flash chromatographic purification (with 10% EtOAc/hexanes as the eluent) (vide supra) provided 83 mg (60% from **3**) of a 14:1 mixture of **4a/4b** (R = cyclohexyl) as a viscous colorless oil. For **4a** (R = cyclohexyl): ^{1}H NMR (360 MHz, $CDCl_3$) δ 0.74 (s, 3 H, 18-H), 0.97 (d, 1 H, J = 7.0 Hz, 21-H), 1.05 (s, 3 H, 19-H), 1.97 (s, 3 H, OAc), 2.03 (s, 3 H, OAc), 4.5–4.7 (m, 1 H, 3-H), 4.92 (dd, 1 H, J = 8.4, 3.7 Hz, 22-H), 5.39 (br d, 1 H, J = 4.7 Hz, 6-H), 5.47 (br s, 1 H, 16-H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 15.75 (q), 19.25 (q), 19.42 (q), 20.82 (t), 21.04 (q), 21.38 (q), 26.01 (t), 26.28 (t), 26.40 (t), 26.50 (t), 27.86 (t), 30.74 (d), 30.99 (d), 31.35 (t), 31.68 (t), 33.25 (d), 34.81 (t), 36.91 (s), 37.04 (t), 38.24 (t), 39.20 (d), 47.32 (s), 50.80 (d), 57.18 (d), 73.96 (d), 79.82 (d), 122.51 (d), 122.61 (d), 139.97 (s), 156.75 (s), 170.38 (s), 170.62 (s); IR ($CHCl_3$) 2930, 1734, 1234 cm^{-1}; HRMS (CI-NH_3, 23 eV) calcd for $[C_{32}H_{48}O_4 \cdot H]$ m/z 497.3631, found 497.3618.

(22*S*)-3β,22-Diacetoxy-5-cholestene (11). A suspension of crude **4a** (R = isoamyl) (100 mg) and 30 mg of 5% Pt/C in ether (10 mL) and EtOH (10 mL) was stirred at rt for 1 h. The mixture was filtered and the solvent was removed by rotary evaporation. The solid thus obtained was recrystallized twice from MeOH to give 69 mg of **11** as a white solid (69%): mp 139–141 °C (MeOH) [lit.[21] mp 143–145 °C]; $[\alpha]^{22}_D$ −51° (*c* 0.80, $CHCl_3$) [lit.[21] $[\alpha]_D$ −57° (*c* 0.10)]; ^1H NMR (360 MHz, $CDCl_3$) δ 0.68 (s, 3 H, 18-H), 0.87 (d, 6 H, *J* = 6.6 Hz, 26/27-H), 1.02 (s, 3 H, 19-H), 2.03 (s, 3 H, OAc), 2.04 (s, 3 H, OAc), 4.52–4.72 (m, 1 H, 3-H), 4.93 (ddd, 1 H, *J* = 7.0, 7.0, 0.73 Hz, 22-H), 5.38 (br d, 1 H, *J* = 4.8 Hz, 6-H).

(22*S*)-3β,22-Diacetoxy-5α-cholestrane (12). A suspension of crude **11** (100 mg) and 30 mg of 5% Pt/C in EtOAc (10 mL) under H_2 atm was stirred at room temperature for 3 h at which time the mixture was filtered and the solvent was removed by rotary evaporation. The crude product was purified by recrystallization from MeOH, yielding 73 mg of **12** as a white solid (73%): mp 122–125 °C (MeOH), [lit.[22] mp 125–127 °C]. $[\alpha]^{22}_D$ −9.5° (*c* 0.93, $CHCl_3$) [lit.[22] $[\alpha]_D$ −10°]. ^1H NMR (360 MHz, $CDCl_3$) δ 0.63 (s, 3 H, 18-H), 0.79 (s, 3 H, 19-H), 0.85 (d, 3 H, *J* = 6.6 Hz, 26/27-H), 0.92 (d, 3 H, *J* = 6.6 Hz, 26/27-H), 1.99 (s, 3 H, OAc), 2.01 (s, 3 H, OAc), 4.55–4.73 (m, 1 H, 3-H), 4.90 (ddd, 1 H, *J* = 6.4, 6.4, 1.0 Hz, 22-H); MS (CI-NH_3, 23 eV) *m/z* 506 (100% $[M + 18]^+$), 446 (4% $[M + 18 - 60]^+$), 429 (12), 369 (30), 316 (56), 152 (35).

Phenyl Adducts 14a/14b. To a solution of bisnorcholenal THP ether **13** (100 mg, 0.242 mmol; prepared from 3β-hydroxy-22,23-bisnorcholenic acid[28] which was purchased from Steraloid, Inc., Wilton, NH) in THF (2 mL) was added 1.0 mL of a PhMgBr solution (2.9 M in ether, 2.9 mmol) at rt. After 6 h the reaction was quenched by the addition of 1 M aqueous HCl (2 mL) and the resulting mixture was kept stirring at rt for 4 h. Extraction with EtOAc (3 × 5 mL) furnished the crude diol. Acetylation of the diol with acetic anhydride and pyridine (vide supra) followed by flash chromatographic purification using 10% EtOAc/hexanes as the eluent provided 90 mg of a 2.5:1 mixture of **14a/14b** as a white solid (70% from **13**). Alternatively, a suspension of the benzaldehyde ene adduct **4b** (R = phenyl) (50 mg) and 10 mg of 5% Pt/C in ether/EtOH (2 mL/2 mL) under H_2 was stirred at rt for 3 h. After filtration and removal of the solvent, 50 mg of **14b** was obtained as a white solid. For **14b**: mp 175–177 °C (MeOH); ^1H NMR (360 MHz, $CDCl_3$) δ 0.71 (s, 3 H, 18-H), 0.89 (d, 3 H, *J* = 6.7 Hz, 21-H), 0.98 (s, 3 H, 19-H), 2.00 (s, 3 H, OAc), 2.07 (s, 3 H, OAc), 4.52–4.65 (m, 1 H, 3-H), 5.35 (m, 1 H, 6-H), 5.82 (d, 1 H, *J* = 3.6 Hz, 22-H), 7.13–7.45 (m, 5 H); IR ($CHCl_3$) 1735 cm^{-1}. MS (CI-CH_4, 23 eV) *m/z* 433 (2.5, $[M + 1 - 60]^+$), 373 (4, $[M + 1 - 120]^+$), 105 (100), 85 (76). Anal. Calcd for $C_{32}H_{44}O_4$: C, 78.01; H, 9.00. Found: C, 78.00; H, 9.19. For **14a**: mp 207–209 °C (MeOH); ^1H NMR (360 MHz, $CDCl_3$) δ 0.68 (s, 3 H, 18-H), 0.83 (d, 1 H, *J* = 6.8 Hz, 21-H), 1.00 (s, 3 H, 19-H), 2.02 (s, 3 H, OAc), 2.15 (s, 3 H, OAc), 4.51–4.65 (m, 1 H, 3-H), 5.36 (m, 1 H, 6-H), 5.96 (d, 1 H, *J* = 0.9 Hz, 22-H), 7.05–7.43 (m, 5 H); IR ($CHCl_3$) 1735 cm^{-1}; MS (CI-CH_4, 23 eV) *m/z* 433 (2, $[M + 1 - 60]^+$), 373 (35, $[M + 1 - 120]^+$), 105 (99), 85 (100).

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(28) Green, D. M.; Edwards, J. A.; Barksdale, A. W.; McMorris, T. C. *Tetrahedron* **1971**, *27*, 1199.