Asymmetric Tandem Claisen-Ene Strategy for Convergent Synthesis of (+)-9(11)-Dehydroestrone Methyl Ether: Stereochemical Studies on the Ene Cyclization and Cyclic Enol Ether Claisen Rearrangement for Steroid Total Synthesis

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Abstract: An asymmetric synthesis of (+)-9(11)-dehydroestrone methyl ether (**1**), a key intermediate for estrogen analogs, is described using a new strategy of consecutive carbocyclizations for the D and C rings of the steroid skeleton based on an asymmetric tandem Claisen-ene sequence. Studies of the stereochemical features of the cyclic enol ether Claisen rearrangement and intramolecular ene reaction are also reported. In the model study of the ene cyclizations, high *trans* diastereofacial selectivity is found for the α-alkylcrotyl and the α,β-dialkylcrotyl ether systems with a methoxycarbonyl group at the acetylenic terminus, which remarkably facilitates the ene cyclization. The Claisen rearrangements of the enol ethers of cyclic ketones were found to exhibit a high level of either *anti* or *syn* diastereoselectivity along with high *E* olefinic stereoselectivity by making judicious use of either 2,6-dimethylphenol or $PdCl_2(RCN)_2$ as the catalyst.

Steroids have played vital roles as target molecules in the development of new synthetic strategies, because of their well-defined structures which provide an opportunity to test new methodologies and explore their stereochemistry.[1,2] The concept of "tandem reaction sequence"[3] has been used for shortening of the synthetic sequence and for relaying of stereochemical control in a multistep synthesis of complex natural products. Herein we report the asymmetric tandem Claisen rearrangement and ene reaction sequence as an efficient strategy for the asymmetric synthesis of (+)-9(11)-dehydroestrone methyl ether (**1**), a key intermediate for estrogens.[4,5] The key transformation is the convergent combination of the A,B and C,D ring synthons by the asymmetric Claisen-ene sequence (**I** → **II** → **III**), which is theorized to proceed with high stereochemical control (Scheme 1). Thus, this tandem strategy investigates two stereochemical questions: (1) diastereoselectivity induced on C-8 and C-14 (steroid numbering) of **II** in the Claisen rearrangements with the cyclic enol ether of steroid A,B-ring component **4**, which should proceed with a high level of 1,3-chirality transfer from C-12 to C-14 in compound **I**,[6] (2) diastereofacial selectivity of the quaternary carbon C-13 (**III**) in the intramolecular ene reaction[7] of substrate **II** having the chiral center C-14 on the ene component rather than the enophile.

Results and Discussion

Diastereofacial Selectivity in Intramolecular Ene Reactions. Our total synthesis was preceded by the investigation of the diastereofacial selectivity of the intramolecular ene reaction of type 5-(3,4)[8] to construct the steroid D ring. The main point of interest was the stereocontrol over the newly created quaternary carbons, which had not been previously explored.[7,8] Furthermore, asymmetric ene cyclizations, hitherto-reported, have used chiral enophiles[9] rather than chiral ene components to induce diastereofacial selectivity.

Allylic propargyl ethers **7** with a variety of substituents were prepared as model ene systems [X = O][10a] by standard methods using phase transfer techniques.[11] Methoxycarbonylation (*n*-

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(1) Reviews: (a) Groen, M. B.; Zeelen, F. J. *Recl. Trav. Chim. Pays-Bas* **1986**, *105*, 465. (b) Taub, D. In *The Total Synthesis of Natural Products*; ApSimon, J., Ed.; John Wiley: New York, 1984; Vol. 6. (c) Blickenstaff, R. T.; Ghosh, A. C.; Wolf, G. C. *Total Synthesis of Steroids*; Academic Press: New York, 1974. (d) Fieser, L. F.; Fieser, M. *Steroids*; Reinhold: New York, 1959.

(2) Recent examples: (a) Horiguchi, Y.; Nakamura, E.; Kuwajima, I. *J. Am. Chem. Soc.* **1989**, *111*, 6257. (b) Takahashi, T.; Shimizu, K.; Doi, T.; Tsuji, J. *J. Am. Chem. Soc.* **1988**, *110*, 2674. (c) Stork, G.; Saccomano, N. A. *Tetrahedron Lett.* **1987**, *28*, 2087. (d) Johnson, W. S.; Lindell, S. D.; Steele, J. *J. Am. Chem. Soc.* **1987**, *109*, 5852. (e) Ziegler, F. E.; Wang, T. F. *J. Am. Chem. Soc.* **1984**, *106*, 718.

(3) Reviews: (a) Ziegler, F. E. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: New York, 1991; Vol. 6, p 875. (b) Mikami, K.; Nakai, T. *Synthesis* **1991**, 594. Nakai, T.; Mikami, K. *Kagaku no Ryoiki* **1982**, *36*, 661; *Chem. Abstr.* **1982**, *96*, 16001. For a recent example of the tandem Claisen-ene reaction, see: Mandai, T.; Matsumoto, S.; Kohama, M.; Kawada, M.; Tsuji, J. *J. Org. Chem.* **1990**, *55*, 5671.

(4) (a) Posner, G. H.; Switzer, C. *J. Am. Chem. Soc.* **1986**, *108*, 1239. (b) Ziegler, F. E.; Lim, H. *J. Org. Chem.* **1982**, *47*, 5230. (c) Posner, G. H.; Mallamo, J. P.; Black, A. Y. *Tetrahedron* **1981**, *37*, 3921. (d) Quinckert, G.; Weber, W. D.; Schwartz, U.; Duerner, G. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 1027; Quinckert, G.; Schwartz, U.; Stark, H.; Weber, W. D.; Baier, H.; Adam, F.; Duerner, G. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 1029.

(5) A preliminary report of this work: Mikami, K.; Takahashi, K.; Nakai, T. *J. Am. Chem. Soc.* **1990**, *112*, 4035.

(6) Excellent review on the chirality transfer via sigmatropic rearrangements: Hill, R. K. In *Asymmetric Synthesis*; Morrison, J. D, Ed.; Academic Press: New York, 1984; Vol. 3.

(7) Reviews on intramolecular ene reactions: (a) Snider, B. B. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: London, 1991; Vols. 2 and 5. (b) Taber, D. F. *Intramolecular Diels-Alder and Alder Ene Reactions*; Springer-Verlag: Berlin, 1984. (c) Oppolzer, W.; Snieckus, V. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 476.

(8) In an intramolecular ene reaction, the carbon numbers, where the tether connects the ene and enophile components constituting the [1,5]-hydrogen shift system, are exemplified in (*m,n*) fashion. The numerical prefix *l* stands for the forming ring size. Thus, the present mode of five-membered ring cyclization can be referred to as 5-(3,4), which corresponds to the five-membered ring cyclization via Oppolzer's type I ene reaction. For the notation of *l*-(*m,n*), see a comprehensive review on ene reactions: Mikami, K.; Shimizu, M. *Chem. Rev.* **1992**, *92*, 1021.

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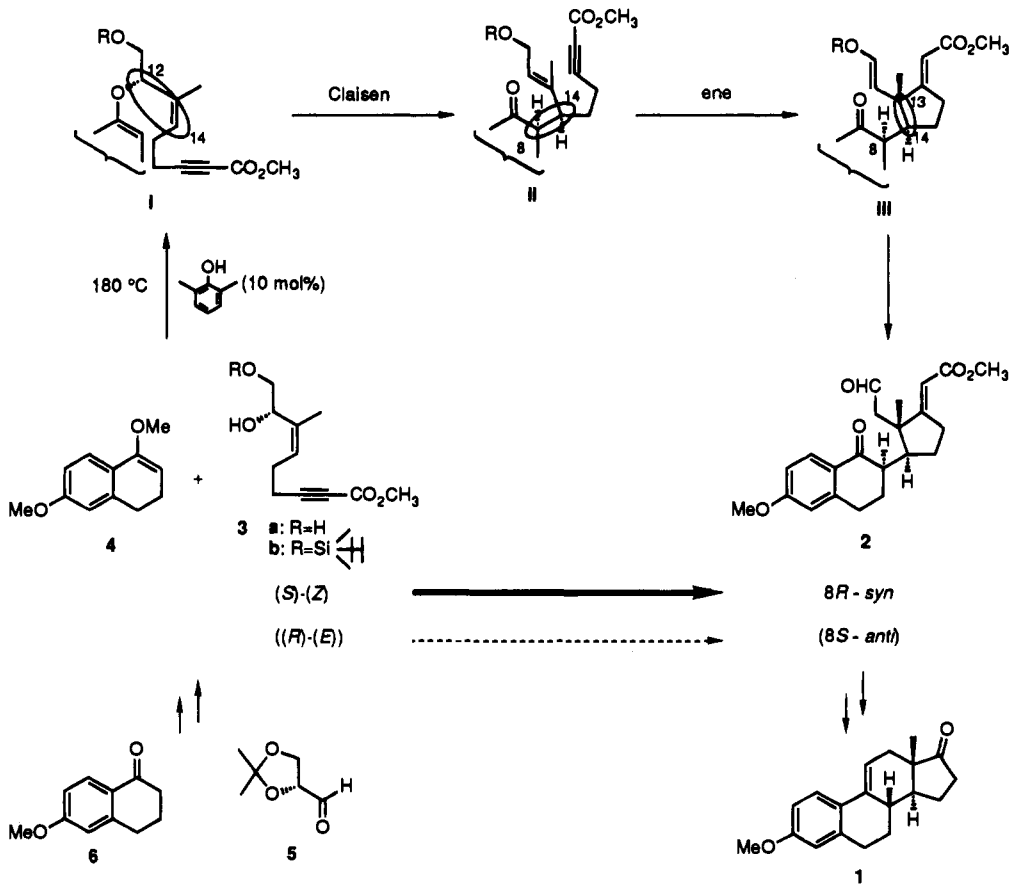
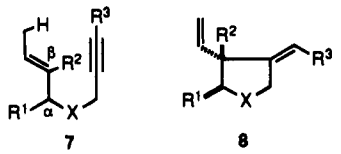
Scheme 1



$BuLi/ClCO_2CH_3$, THF, −78 °C)[12] of the propargyl ethers **7** gave the ester derivatives **7′**. The ene cyclizations of the propargyl ethers **7** and **7′** were run on heating in sealed tubes. The *trans* configuration of the major diastereomer was assigned through comparison of its ^{13}C NMR spectrum with that of the minor diastereomer; the configuration of the isomer in which C-α resonates at a lower field was assigned as *trans*.[13] Table 1 summarizes the products **8** and their relative stereochemistry, which reveals the following significant features of those ene cyclizations.



7

8

(1) The ene cyclization is markedly enhanced by the introduction of an electron-withdrawing ester group at the acetylenic terminus (*e.g.*, entry 1 vs 2).[10d]

(2) Relatively high levels of 1,2-asymmetric induction, *i.e.*, *trans* diastereofacial selection, were observed (entries 3−7). Particularly noteworthy is that the remarkably high selectivity is obtained with the substrates bearing the bulky α-substituents (entries 4−7).

(3) It should be noted here that quaternary carbons can be generated with high levels of *trans* diastereofacial selectivity as observed with the β-methylcrotyl ether systems (entries 6 and 7).

The high *trans* diastereofacial selectivity is desired in the stereoselective construction of the steroid D ring and hence is of mechanistic importance. The *trans* diastereofacial selectivity may be reasonably explained in terms of ab initio MM2 transition state models **A** and **B**.[14] Of the two transition states **A** and **B**, transition state **A** leading to the *trans* configuration is sterically less congested than transition state **B** leading to the

Table 1. Thermal Ene Cyclization

entry	ether	R^1	R^2	R^3	temp (°C)/ time (h)	product	% yield[a]	*trans*: *cis*[b]
1	**7a**	H	H	H	250/6	**8a**	95	
2	**7′b**	H	H	CO_2Me	200/1	**8b**	98	
3	**7′c**	Me	H	CO_2Me	130/24	**8c**	90	86:14
4	**7′d**	*i*-Pr	H	CO_2Me	130/24	**8d**	90	>95:<5
5	**7′e**	Ph	H	CO_2Me	130/24	**8e**	97	93:7
6	**7′f**	*i*-Pr	Me	CO_2Me	130/24	**8f**	93	90:10
7	**7′g**	Ph	Me	CO_2Me	130/24	**8g**	88	92:8

[a] Isolated yield after column chromatography. [b] Determined by HPLC (Zorbax SIL, hexane/ethyl acetate) and/or ^1H NMR.

(9) (a) Townsend, C. A.; Scholl, T.; Arigoni, D. *J. Chem. Soc., Chem. Commun.* **1975**, 921. (b) Nakatani, Y.; Kawashima, K. *Synthesis* **1978**, 147. (c) Oppolzer, W.; Robbiani, C.; Battig, K. *Helv. Chim. Acta* **1980**, *63*, 2015; *Tetrahedron* **1984**, *40*, 1391. (d) Tietze, L.-F.; Kiedrowski, G. V. *Tetrahedron Lett.* **1982**, *22*, 219. (e) Oppolzer, W.; Thirring, K. *J. Am. Chem. Soc.* **1982**, *104*, 4978. (f) Smith, A. B. III; Fukui, M. *J. Am. Chem. Soc.* **1987**, *109*, 1269. (g) Funakoshi, K.; Sakai, K.; Hata, T.; Tamura, C. *Tetrahedron Lett.* **1989**, *30*, 4849 and references cited therein.

(10) (a) Mikami, K.; Takahashi, K.; Nakai, T. *Chem. Lett.* **1987**, 2347. A few reports have appeared on similar 5-(3,4) ene cyclizations of related substrates: (b) [X = NR] Oppolzer, W.; Pfenninger, E.; Keller, K. *Helv. Chim. Acta* **1973**, *56*, 1807. (c) [$X = CH_2$] Reference 9a. (d) Snider, B. B.; Killinger, T. A. *J. Org. Chem.* **1978**, 43, 2161. (e) [$X = C(CN)OSiR_3$)] Stork, G.; Kraus, G. *J. Am. Chem. Soc.* **1976**, *98*, 6747.

(11) Mikami, K.; Azuma, K.; Nakai, T. *Tetrahedron* **1984**, *46*, 2303.

(12) Taschener, M. J.; Rosen, T.; Heathcock, C. H. *Org. Synth.* **1985**, *64*, 108.

(13) Eliel, E. L.; Rao, V. S.; Dietrusiewicz, K. M. *Org. Magn. Reson.* **1979**, *12*, 461.

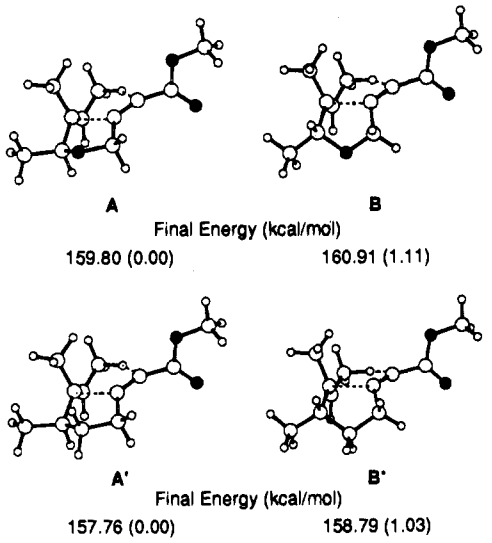
(14) Houk, K. N.; Paddon-Row, M. N.; Rondan, N. G.; Wu, Y. D.; Brown, F. K.; Spellmeyer, D. C.; Metz, J. T.; Li, Y.; Loncharich, R. *Science* **1986**, *231*, 1108.

Table 2. Cyclic Enol Ether Claisen Rearrangements

entry	alcohol	enol ether	catalyst	temp (°C)/time (h)	product	% yield[a]	*anti*/*syn*[b]
1	(*E*)-**9a** (R = H)[c]	**4**	$Hg(OAc)_2$	140/10	**11a**	95	61:39
2				100/17		91	77:23
3			DMP	100/17		94	94:6
4			$PdCl_2(PhCN)_2$	rt/3		95	13:87
5	(*Z*)-**9a** (R = H)[d]		DMP	100/17		95	15:85
6			$PdCl_2(PhCN)_2$	rt/24		40[e]	21:79
7	(*E*)-**9b** (R = *i*-Bu)[f]		DMP	100/10	**11b**[g]	95	>95:<5
8			$PdCl_2(PhCN)_2$	rt/1		95	<5:>95
9	(*E*)-**9a** (R = H)[c]	**10**	DMP	120/14	**12a**	95	88:12
10[h]			$PdCl_2(MeCN)_2$	rt/10		78	12:88
11	(*Z*)-**9a** (R = H)[d]		DMP	120/14		95	25:75
12	(*E*)-**9c** (R = Me)[i]		DMP	120/14	**12c**[g]	95	81:19
13	(*Z*)-**9c** (R = Me)[j]		DMP	120/14		95	11:89

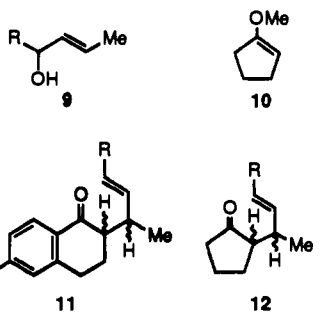
[a] Isolated yield after column chromatography. [b] The stereoisomeric ratio was determined by HPLC (Zorbax SIL, hexane/ethyl acetate) and/or ^1H NMR. [c] 94% *E*. [d] 93% *Z*. [e] The reaction was quite sluggish because of the *Z* → *E* isomerization. [f] 100% *E*. [g] The (*E*)-olefin was formed exclusively. [h] The substrate used is 1-(crotyloxy)-1-cyclopentene which was prepared by a literature procedure: Takai, K.; Mori, I.; Oshima, K.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 446. [i] 94% *E*. [j] 98% *Z*.

cis configuration, as shown by the calculated steric energies (X = O or X = CH_2 (**A**′ vs **B**′)).



Diastereoselectivity in Cyclic Enol Ether Claisen Rearrangements. Our strategy for steroid synthesis employs a cyclic enol ether which triggers the tandem Claisen–ene sequence (Scheme 1). The Claisen rearrangement is an important synthetic tool for acyclic stereocontrol, wherein the olefinic stereocontrol of the enol ether part is the key to diastereocontrol over the newly created chiral centers of the product.[15] Previous work has shown that the acyclic enol ether Claisen variants show only low diastereoselectivity because of the lack of olefinic stereoselectivity in the allylic enol ether formation. By contrast, the cyclic (stereodefined) enol ether Claisen variant would provide a high level of diastereoselectivity.[16] Furthermore, we have found that the judicious choice of the catalyst employed, 2,6-dimethylphenol (DMP) or $PdCl_2(RCN)_2$, permits the highly stereoselective formation of either the *syn* or *anti* product.[17a]

Table 2 summarizes the results of the Claisen rearrangements of allylic alcohols **9a–c** with the two types of cyclic enol ethers **4**[18] and **10**.[19] All the Claisen rearrangements were carried out in toluene solutions of the allylic alcohols and cyclic enol ethers (0.2 M each) in the presence of the catalyst (10 mol %) [$Hg(OAc)_2$, DMP, or $PdCl_2L_2$ (L = PhCN or MeCN)]. Table 2 reveals several significant features of these cyclic enol ether Claisen variants.



(1) The conventional Claisen procedure using the catalyst $Hg(OAc)_2$ shows only a moderate *syn*/*anti* selectivity (entries 1 and 2), presumably because the acetic acid once formed causes epimerization.[20]

(2) The rearrangement catalyzed by DMP exhibits a remarkably enhanced *anti* selectivity when employing the *E* allylic alcohol (entries 3, 7, 9, and 12) and hence *syn* selectivity when employing the *Z* counterpart (entries 5, 11, and 13). Apparently, the lower acidity of DMP is responsible for the enhanced stereoselectivity.

(3) Surprisingly enough, the Pd(II)-catalyzed rearrangement not only proceeds smoothly even at room temperature but also exhibits the opposite stereoselectivity, *i.e.*, the *E* allylic alcohol induces *syn* selectivity (entries 4, 8, and 10). Unfortunately, no rearrangement occurred with β-substituted allylic alcohols such as the chiral allylic alcohol **3**. This failure parallels the significant limitation reported for the Pd(II)-catalyzed Cope rearrangement of 2,5-disubstituted 1,5-dienes.[21]

(15) Comprehensive review on the Claisen rearrangements: Ziegler, F. E. *Chem. Rev.* **1988**, *88*, 1423.

(16) The Claisen variant with cyclic orthoesters has been reported. Review: Lythgoe, B. *Chem. Soc. Rev.* **1981**, *10*, 449.

(17) (a) Mikami, K.; Takahashi, K.; Nakai, T. *Tetrahedron Lett.* **1987**, *28*, 5879. After completion of this work, two reports dealing with the Claisen variant with ketals of cyclic ketones appeared: (b) Baan, J. L.; Bickelhaupt, F. *Tetrahedron Lett.* **1986**, *27*, 6267. (c) Daub, G. W.; Griffith, D. A. *Tetrahedron Lett.* **1986**, *27*, 6311. Also see: Ziegler, F. E.; Klein, S. I.; Pati, U. K.; Wang, T.-F. *J. Am. Chem. Soc.* **1985**, *107*, 2730.

(18) The enol ether **4** was prepared in 86% isolated yield by applying a literature procedure: Miller, R. B.; Gutierres, C. G. *J. Org. Chem.* **1978**, *43*, 1569.

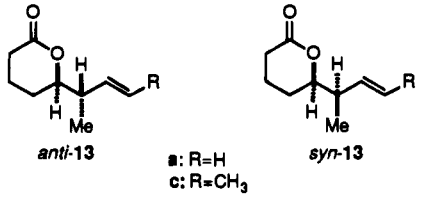
(19) Prepared in 84% isolated yield following a literature procedure: Wohl, R. A. *Synthesis* **1974**, 38.

(20) After completion of this work, the *syn*/*anti* selectivity of the cyclic ketal Claisen rearrangement was reported to be attenuated by propionic acid via epimerization of the product (ref 17c).

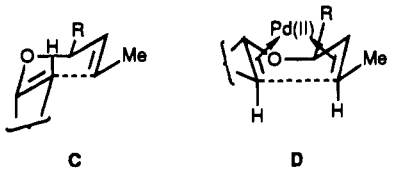
(21) Reviews on catalysis of the Cope and Claisen rearrangement: Overman, L. E. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 579. (b) Lutz, R. P. *Chem. Rev.* **1984**, *84*, 205.

(4) In all cases where an internal olefin is formed, an extremely high *E* selectivity is observed for both the DMP- and Pd(II)-catalyzed rearrangements (entries 7, 8, and 12). Thus, the extremely high level of 1,3-chirality transfer would be expected[6] in the cyclic enol ether Claisen rearrangements.

The stereochemical assignment of the diastereomeric Claisen products deserves special comment. The product stereochemistry in the conventional Hg(II)- and acid-catalyzed Claisen processes is readily assignable to the *E* → *anti* configuration based on the well-established chairlike transition states.[6,15] The stereochemistry of **12c** was further confirmed through its conversion to the known pentanolide diastereomer **13c**[22] via Baeyer–Villiger oxidation with peracetic acid. The comparison showed that *syn*-**12c**, where the 1′-methyl NMR signal appeared at a lower field than that of *anti*-**12c**, was correlated to *syn*-**13c**, where the oxymethine NMR signal appeared at a higher field as compared to that of *anti*-**13c**. The stereochemistry of **12a** was also confirmed through its similar conversion to the pentanolide **13a** which exhibited a similar trend in the NMR to that of **13c**. The stereochemical assignments of **11a** and **11b** were made on the basis of similar NMR trends to those observed for **12a** and **12c**. Furthermore, it should be noted that the *syn*/*anti* pairs of all the products **11** and **12** showed similar differences in their HPLC retention times; *syn* diastereomers had longer retention times than *anti* diastereomers.



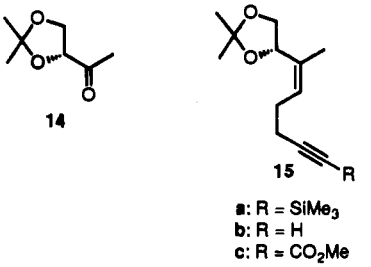
Particularly noteworthy is the dramatic switch in diastereoselectivity observed by changing the catalyst from DMP to $PdCl_2(RCN)_2$. The *E* → *anti* selectivity of the DMP-catalyzed rearrangement is easily visualized by the well-established chairlike transition state **C**, whereas the *E* → *syn* selectivity of the Pd(II)-catalyzed rearrangement can be explained by the boatlike transition state **D** where the diene moiety may act as a bidentate ligand. Previously, a similar boatlike transition state was proposed for the $PdCl_2(PhCN)_2$-catalyzed Cope rearrangement of *cis*-1,2-divinylcyclobutane.[23] Thus, the DMP- and Pd(II)-catalyzed cyclic enol ether Claisen rearrangements constitute stereocomplementary processes for the addition of acyclic side chains onto the α-position of cyclic ketones.



C **D**

Asymmetric Tandem Claisen–Ene Reaction. We studied the preparation of the starting chiral allylic alcohol for the asymmetric tandem Claisen–ene reaction. To introduce the 14*S* chirality into the Claisen product **II**, either (*R*,*E*)-**3** or (*S*,*Z*)-**3**, which respectively leads to 8*S*-*anti* or 8*R*-*syn* diastereomers, is required (Scheme 1). We decided on (*S*,*Z*)-**3** because it is readily available from (*R*)-glyceraldehyde **5** by using the highly *Z* selective Still–Wittig olefination.[24] More importantly, Ziegler has already reported that the *syn* diastereomer can be stereoselectively transformed via the epimerization at C-8 to the desired *anti* diastereomer.[4b]

The Still–Wittig olefination of methyl ketone **14**[25] was carried out in THF without the use of HMPA as a cosolvent[24] at −78 °C using [5-(trimethylsilyl)-4-pentynyl]phosphonium salt and *n*-BuLi to afford, after desilylation (*n*-Bu_4NF), (*Z*)-enyne **15b** (R = H) exclusively. When the reaction was done at −30 °C, ca. 5% of the *E* isomer was formed ($\delta_{3\text{-Me}}$ 1.73 ppm for (*Z*)-**15b** and 1.63 ppm for (*E*)-**15b**). Methoxycarbonylation (*n*-BuLi/$ClCO_2CH_3$, THF, −78 °C)[12] of **15b** followed by deprotection of the acetonide (*p*-TsOH, MeOH) and selective protection of the primary hydroxyl group with dimethylthexylsilyl chloride (DMF, imidazole, −40 °C) gave stereochemically pure (*S*,*Z*)-**3b** in 86% overall yield from **5**.



Now, the stage was set for the one-pot Claisen–ene sequence. A toluene solution of **3b** (the C,D-ring component) and the cyclic enol ether **4** (the A,B-ring component) in the presence of DMP (10 mol %) was heated in a sealed tube at 180 °C for 60 h. The tandem Claisen–ene product **2** was isolated in 76% yield after hydrolysis (1 N HCl, THF). A careful NMR analysis (500 MHz) of **2** showed that the 13,14-configuration was predominantly *trans* and the 8,14-configuration was 90% *syn*.[26] The transformation of the tandem product to the estrogen skeleton was accomplished following Ziegler's procedure.[4b] Ozonolysis (O_3, MeOH, −35 °C, Me_2S) of **2** afforded Ziegler's diketoaldehyde **16** (*syn*:*anti* = 9:1) in 67% yield. The use of CH_2Cl_2 or CH_2Cl_2/MeOH as the solvent was found to afford a complex mixture. The isomeric mixture was subjected to epimerization at C-8 (NaOMe/MeOH, 25 °C)[4b] to give an *anti*-rich mixture (*syn*:*anti* = 1:4). The desired 8H_β isomer *anti*-**16** was isolated in 69% yield. Application of the modified McMurry coupling reaction ($TiCl_3$/Zn(Ag), DME)[27] to *anti*-**16** for the C-ring construction furnished the desired compound **1** in 56% isolated yield. Its physical and spectral data were in accord with the literature values: $[\alpha]^{21}_D$ +258° (*c* 0.70, $CHCl_3$), mp 144–145 °C (EtOAc/EtOH) [lit.[4a] $[\alpha]^{25}_D$ +247.2° (>97.3% ee) (*c* 0.50, $CHCl_3$), mp 144–145 °C]. The optical purity of **1** was 100% ee as judged from the reported $[\alpha]_D$ value. The overall yield of **1** was 17% in 5 steps from 6-methoxy-1-tetralone (**6**) and in 11 steps from (*R*)-glyceraldehyde **5**.

Conclusions

In summary, the key feature of the present strategy is the successful combination of the asymmetric Claisen rearrangement

(22) For the ^1H NMR data of the pentanolide diastereomers **13c**, see: S.-Rouvier, C. *Tetrahedron Lett.* **1984**, *25*, 4371.

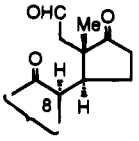
(23) Heimbach, P.; Molin, M. *J. Organomet. Chem.* **1973**, *49*, 477.

(24) Streekumar, C.; Durst, K. P.; Still, W. C. *J. Org. Chem.* **1980**, *45*, 4260.

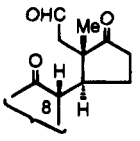
(25) The ketone **14** was prepared from **5** via the standard method [MeMgI, DMSO, $(COCl)_2$, Et_3N]; $[\alpha]^{26}_D$ +74.1° [lit. $[\alpha]^{20}_D$ +53.3°]: Dumont, R. *Helv. Chim. Acta* **1983**, *66*, 814.

(26) The aldehyde protons of 8H_α-**2** and 8H_β-**2** were observed at δ 9.70 and 9.45 ppm, respectively. The *trans*,*syn* configuration of **2** thus deduced was confirmed after transformation to the known *trans*,*syn*-diketoaldehyde **16** (ref 4b).

(27) (a) McMurry, J. E. *Chem. Rev.* **1989**, *89*, 1513. (b) Lenoir, D. *Synthesis* **1989**, 883.



syn-16



anti-16

and ene reaction in tandem for the carbocyclization of the D ring that allows for a relatively quick construction of the estrogen framework in a highly stereocontrolled fashion.[28] Particularly noteworthy are the stereochemical outcomes of the asymmetric tandem sequence: (1) high levels of chirality transfer and diastereoselectivity in the cyclic enol ether Claisen rearrangement which serves as an efficient process for asymmetric addition of acyclic side chains onto the α-position of cyclic ketones, (2) high *trans* diastereofacial selectivity even for the construction of the quaternary centers in the 5-(3,4) ene carbocyclization. Finally, the present approach to the 9(11)-steroidal skeleton permits easy access to 11-oxygenated estrogens having pronounced biological activities[29] as well as 19-norcorticoids through the utilization of the 17-side chain of **2**.[30]

Experimental Section

General Procedures. IR spectra were recorded on a JASCO A-102 spectrophotometer. Polarimetric analyses were run on a JASCO DIP-140 polarimeter. NMR spectra were taken on Varian EM-390, JEOL FX-90Q, JEOL GX-270, Varian Gemini 200, and JEOL GX-500 spectrometers and reported in parts per million downfield from internal TMS in $CDCl_3$. GLC analyses were run on a Shimadzu GC-3BT chromatograph by using helium as the carrier gas and a 3 mm × 3 m stainless steel column packed with PEG-20M and SE-30 and a Shimadzu GC-8A chromatograph by using nitrogen as the carrier gas and a 0.24 mm × 50 m glass capillary column packed with ULBON HR-20 at the indicated temperature. HPLC analyses were run on a JASCO TRIROTAR SR-1 pump, equipped with a 4.6 mm × 250 mm Finepak SIL-5 column using Shimadzu RID-6A as a refractive index detector and on a Shimadzu LC-6A pump equipped with a 4.6 mm × 250 mm Zorbax SIL column and Shimadzu RID-6A as a refractive index detector. Analytical TLC was performed by using Merck precoated TLC plates and 60F-254 silica gel with indicator. Column chromatography was performed by using Wakogel C-200 (Wako) and Kiesegel 60 (Merck). Elemental analyses were performed by YANACO CHN CORDER MT-3. Mass spectra were obtained on a JEOL JMS-300.

Materials. Tetrahydrofuran (THF), diethyl ether, and 1,2-dimethoxyethane (DME) were predried with $LiAlH_4$ and distilled over benzophenone ketyl under a nitrogen atmosphere prior to use. Toluene and methanol were purified from sodium under a nitrogen atmosphere. Dichloromethane, dimethyl sulfoxide (DMSO), dimethylformamide (DMF), and triethylamine (TEA) were dried from CaH_2 under a nitrogen atmosphere.

Synthesis of Carbomethoxy Ethers 7′.[12] To a solution of allyl propargyl ether **7**[11] in THF was added dropwise a hexane solution of *n*-BuLi (1.05 molar ratio) at −78 °C under argon atmosphere, and the mixture was stirred at that temperature for 1 h. Methyl chloroformate (1.5 molar ratio) was added to the mixture, and the resulting mixture was warmed to room temperature and stirred for 2 h. To this mixture aqueous NH_4Cl was added, and the mixture was extracted with ether, washed with brine, and dried over magnesium sulfate. Removal of the solvent followed by column chromatography on silica gel gave carbomethoxy ethers **7′**.

Methyl 4-(2(*E*)-Buten-1-yloxy)-2-butynoate (7′b): ^{1}H NMR (90 MHz) δ 1.71 (d, 3H, *J* = 5.1 Hz), 3.72 (s, 3H), 3.94 (d, 2H, *J* = 5.7 Hz), 4.70 (s, 2H), 5.3−5.9 (m, 2H); IR 2950, 2210, 1710, 1430, 1350, 1250, 1100, 1050, 970, 935, and 890 cm^{-1}.

Methyl 4-(3(*E*)-Penten-2-yloxy)-2-butynoate (7′c): ^{1}H NMR (90 MHz) δ 1.27 (d, 3H, *J* = 6.9 Hz), 1.74 (dd, 3H, *J* = 6.3, 1.0 Hz), 3.81 (s, 3H), 4.00 (dq, 1H, *J* = 6.9, 6.9 Hz), 4.24 (s, 2H), 5.30 (ddq, 1H, *J* = 15.0, 8.7, 1.0 Hz), 5.74 (dd, 1H, *J* = 15.0, 6.3 Hz); IR 2960, 2880, 2250, 1720, 1440, 1260, 1100, 970, and 940 cm^{-1}.

Methyl 4-(2-Methyl-4(*E*)-hexen-2-yloxy)-2-butynoate (7′d): ^{1}H NMR (90 MHz) δ 0.85 and 0.93 (2d, 6H, *J* = 6.8 Hz), 1.75 (dd, 3H, *J* = 6.3, 1.3 Hz), 1.6−2.0 (m, 1H), 3.48 (dd, 1H, *J* = 8.3, 6.6 Hz), 3.83 (s, 3H), 4.0−4.4 (m, 2H), 5.0−6.0 (m, 2H); IR 2960, 2240, 1720, 1435, 1260, 1090, 1055, 975, and 750 cm^{-1}; HRMS *m/z* calcd for $C_{12}H_{18}O_3$ 210.1256, found 210.1292.

Methyl 4-(1-Phenyl-2(*E*)-buten-1-yloxy)-2-butynoate (7′e): ^{1}H NMR (90 MHz) δ 1.74 (d, 3H, *J* = 5.7 Hz), 3.80 (s, 3H), 4.24 (s, 2H), 4.94 (d, 1H, *J* = 6.3 Hz), 5.4−6.0 (m, 2H), 7.2−7.6 (m, 5H); IR 2950, 2240, 1720, 1600, 1495, 1435, 1260, 1050, 970, 750, and 700 cm^{-1}; HRMS *m/z* calcd for $C_{15}H_{16}O_3$ 246.1100, found 244.1122.

Methyl 4-(2,4-Dimethyl-4(*E*)-hexen-3-yloxy)-2-butynoate (7′f): ^{1}H NMR (90 MHz) δ 0.75 and 1.02 (2d, 6H, *J* = 8.0 Hz), 1.51 (br s, 3H), 1.64 (d, 3H, *J* = 8.4 Hz), 1.4−2.0 (m, 1H), 3.22 (d, 1H, *J* = 6.6 Hz), 3.80 (s, 3H), 3.9−4.3 (m, 2H), 5.2−5.6 (m, 1H); IR 2970, 2240, 1750, 1720, 1440, 1260, 1090, 1060, 950, 820, and 750 cm^{-1}.

Methyl 4-(2-Methyl-1-phenyl-2(*E*)-buten-1-yloxy)-2-butynoate (7′g): ^{1}H NMR (90 MHz) δ 1.43 (br s, 3H), 1.67 (d, 3H, *J* = 6.9 Hz), 3.80 (s, 3H), 4.27 (s, 2H), 4.91 (s, 1H), 5.6−5.9 (m, 1H), 7.2−7.5 (m, 5H); IR 2970, 2240, 1720, 1600, 1500, 1440, 1380, 1260, 1050, 940, 820, and 750 cm^{-1}.

General Procedure for the Ene Cyclization of Ether 7′. An argon-purged NMR tube or Pyrex glass tube was charged with 0.3 or 3 mL of benzene-d_6 or toluene containing 0.25 or 2 mmol of ene substrate **7′**, respectively. The tube was then flushed with argon and sealed. The sealed tube was immersed to 2/3 of its length and heated in an oil bath at the desired temperature (as monitored by NMR, TLC, and/or GLC analyses). The tube was opened, and the ene products **8** were isolated by column chromatography on silica gel.

3-Ethenyl-4-methylenetetrahydrofuran (8a): ^{1}H NMR (90 MHz) δ 3.0−3.4 (m, 1H), 3.33 (dd, 1H, *J* = 8.0, 8.0 Hz), 3.85 (dd, 1H, *J* = 8.0, 8.0 Hz), 4.10 (t, 2H, *J* = 1.6 Hz), 4.5−5.8 (m, 5H).

3-Ethenyl-4(*Z*)-(carbomethoxymethylene)tetrahydrofuran (8b): ^{1}H NMR (90 MHz) δ 3.74 (s, 3H), 3.4−4.9 (m, 5H), 5.0−5.6 (m, 4H); IR (neat) 2960, 1720, 1670, 1435, 1355, 1210, 1110, 1080, and 935 cm^{-1}.

3-Ethenyl-4(*Z*)-(carbomethoxymethylene)-2-methyltetrahydrofuran (8c): IR (neat) 2960, 1720, 1435, 1355, 1210, 1090, 1000, and 930 cm^{-1}; ^{1}H NMR (90 MHz) (*trans*-**8c**) δ 1.34 (d, 3H, *J* = 6.3 Hz), 2.7−3.0 (m, 1H), 3.74 (s, 3H), 3.4−3.8 (m, 1H), 4.5−4.9 (m, 6H), (*cis*-**8c**) δ 1.13 (d, 3H, *J* = 6.3 Hz), 3.2−3.45 (m, 1H).

3-Ethenyl-4(*Z*)-(carbomethoxymethylene)-2-isopropyltetrahydrofuran (8d): IR (neat) 2930, 1710, 1430, 1350, 1215, 1010, 920, and 700 cm^{-1}; ^{1}H NMR (90 MHz) (*trans*-**8d**) δ 1.00 (d, 6H, *J* = 6.8 Hz), 1.6−2.0 (m, 1H), 3.0−3.3 (m, 1H), 3.3−3.6 (m, 1H), 3.70 (s, 3H), 4.3−5.9 (m, 6H), (*cis*-**8d**) δ 0.79 and 0.95 (2d, 6H, *J* = 6.8 Hz), 1.5−2.0 (m, 1H), 3.2−3.5 (m, 2H), 3.70 (s, 3H), 4.3−6.0 (m, 6H); ^{13}C NMR (*trans*-**8d**) δ 166.6, 136.0, 128.1, 118.9, 112.0, 87.7, 71.2, 53.7, 51.2, 30.9, 19.3, and 17.8, (*cis*-**8d**) δ 166.3, 134.4, 128.1, 117.0, 112.4, 87.4, 71.1, 53.5, 51.1, 28.8, 19.9, and 18.5.

3-Ethenyl-4(*Z*)-(carbomethoxymethylene)-2-phenyltetrahydrofuran (8e): IR (neat) 2960, 1715, 1665, 1435, 1355, 1260, 1220, 1030, 755, and 700 cm^{-1}; HRMS *m/z* calcd for $C_{15}H_{16}O_3$ 246.1100, found 244.1133; ^{1}H NMR (90 MHz) (*trans*-**8e**) δ 3.0−3.3 (m, 1H), 3.76 (s, 3H), 4.2−4.6 (m, 7H), 6.9−7.6 (m, 5H), (*cis*-**8e**) δ 3.4−3.8 (m, 1H), 3.70 (s, 3H), 4.2−4.6 (m, 7H), 6.9−7.6 (m, 5H); ^{13}C NMR (*trans*-**8e**) δ 166.3, 165.2, 139.1, 133.6, 128.2, 127.9, 126.2, 120.3, 112.0, 84.6, 71.7, 58.7, and 51.1, (*cis*-**8e**) δ 166.3, 165.2, 139.1, 134.3, 129.5, 128.0, 126.4, 121.9, 114.9, 82.7, 71.3, 55.4, and 52.6.

(28) Posner has also reported the efficient asymmetric synthesis of **1**, which is transformed (Et_3SiH/CF_3CO_2H) to estrone methyl ether in 90% yield (ref 4c), via eight steps in 7.0% overall yield from 6-methoxy-1-tetralone (**6**) through the Michael addition reaction to the *enantiopure* cyclopentenone sulfoxide (ref 4a).

(29) (a) Gabbard, R. B.; Harmer, L. F.; Segaloff, A. *Steroids* **1981**, *37*, 243. (b) Schoenamon, K.; Van Vielt, N.; Zeelen, F. J. *Eur. J. Med. Chem.* **1980**, *15*, 333.

(30) Review: Livingston, D. A. In *Advances in Medicinal Chemistry*; Maryanoff, B. E., Maryanoff, C. A., Eds.; JAI Press: London; 1992; Vol. 1. Hogg, J. A.; Beal, P. F.; Nathan, A. H.; Lincoln, F. H.; Schneider, W. P.; Magerlein, B. J.; Hanze, A. R.; Jackson, R. W. *J. Am. Chem. Soc.* **1955**, *77*, 4436. Also see: Johnson, W. S.; Eschener, S.; Metcalf, B. W. *J. Am. Chem. Soc.* **1976**, *98*, 1039.

3-Ethenyl-4(*Z*)-(carbomethoxymethylene)-2-isopropyl-3-methyltetrahydrofuran (8f): IR (neat) 2950, 1720, 1660, 1430, 1350, 1220, 1165, 1060, 1010, and 680 cm^{-1}; ^1H NMR (500 MHz) (*trans*-**8f**) δ 0.82 and 1.05 (2d, 6H, J = 6.8 Hz), 1.17 (s, 3H), 1.7−1.9 (m, 1H), 3.19 (d, 1H, J = 9.4 Hz), 3.69 (s, 3H), 4.62 (dd, 1H, J = 18.0, 2.6 Hz), 5.00 (dd, 1H, J = 18.0, 2.6 Hz), 5.22 (d, 1H, J = 16.7 Hz), 5.23 (d, 1H, J = 11.5 Hz), 5.57 (t, 1H, J = 2.6 Hz), 5.75 (dd, 1H, J = 16.7, 11.5 Hz), (*cis*-**8f**) δ 0.90 and 1.03 (2d, 6H, J = 6.8 Hz), 1.32 (s, 3H), 1.7−1.9 (m, 1H), 3.13 (d, 1H, J = 8.6 Hz), 3.70 (s, 3H), 4.6−4.7 (m, 2H), 5.0−5.1 (m, 1H), 5.2−5.3 (m, 1H), 5.61 (t, 1H, J = 2.6 Hz), 5.90 (dd, 1H, J = 17.5, 10.7 Hz); ^{13}C NMR (*trans*-**8f**) δ 172.1, 166.8, 142.0, 114.6, 111.0, 91.6, 70.6, 52.8, 51.1, 29.6, 21.1, 19.1, and 17.9, (*cis*-**8f**) δ 171.4, 166.8, 138.8, 113.6, 111.6, 93.0, 70.6, 54.3, 52.6, 29.5, 21.9, 18.9, and 13.0.

3-Ethenyl-4(*Z*)-(carbomethoxymethylene)-3-methyl-2-phenyltetrahydrofuran (8g): IR (neat) 2950, 1720, 1430, 1370, 1240, 1190, 1100, 1040, 940, 720, and 700 cm^{-1}; HRMS m/z calcd for $C_{16}H_{18}O_3$ 258.1256, found 258.1261; ^1H NMR (*trans*-**8g**) δ 0.83 (s, 3H), 3.75 (s, 3H), 4.71 (s, 1H), 4.9−6.1 (m, 6H), 7.2−7.4 (m, 5H), (*cis*-**8g**) δ 1.30 (s, 3H), 3.75 (s, 3H), 4.72 (s, 1H), 4.9−6.1 (m, 6H), 7.2−7.4 (m, 5H).

General Procedure for the Claisen Rearrangement. A solution of a catalyst (0.1 mmol) in toluene (1 mL) was stirred for 15 min at room temperature under a nitrogen atmosphere. To this solution was added a solution of allylic alcohol (1 mmol) and enol ether (1.2 mmol) in toluene (3 mL), and the resulting mixture was stirred at the described temperature. After the reaction completed, the reaction mixture was filtered through Florisil. Removal of the solvent followed by silica gel column chromatography afforded the rearranged product.

2-(3-Buten-2-yl)-6-methoxy-1,2,3,4-tetrahydronaphthalen-1-one (11a): IR (neat) 2950, 1670, 1600, 1500, 1450, 1340, 1250, 1160, 1120, 1030, 1000, 915, 880, 850, 830, and 760 cm^{-1}; ^1H NMR (90 MHz) (*anti*-**11a**) δ 0.99 (d, 3H, J = 7.2 Hz), 1.6−2.6 (m, 4H), 2.9−3.3 (m, 2H), 3.83 (s, 3H), 4.9−5.3 (m, 2H), 5.91 (ddd, 1H, J = 18.0, 10.2, 6.6 Hz), 6.69 (d, 1H, J = 2.4 Hz), 6.80 (dd, 1H, J = 8.7, 2.4 Hz), 8.01 (d, 1H, J = 8.7 Hz), (*syn*-**11a**) δ 1.10 (d, 3H, J = 7.2 Hz), 1.5−2.3 (m, 4H), 2.8−3.1 (m, 2H), 3.83 (s, 3H), 4.8−5.1 (m, 2H), 5.72 (ddd, 1H, J = 17.7, 10.4, 7.4 Hz), 6.64 (d, 1H, J = 2.4 Hz), 6.78 (dd, 1H, J = 8.7, 2.4 Hz), 8.00 (d, 1H, J = 8.7 Hz); ^{13}C NMR (*anti*-**11a**) δ 197.4, 163.4, 146.4, 142.6, 129.9, 126.8, 114.4, 113.8, 112.4, 55.4, 52.1, 35.7, 29.5, 23.8, and 14.5, (*syn*-**11a**) δ 197.8, 163.4, 146.2, 141.1, 129.9, 126.6, 114.4, 113.1, 112.4, 55.3, 52.4, 36.0, 28.5, 24.6, and 17.6; HPLC (Zorbax SIL, hexane:ethyl acetate = 15:1, flow rate 1.0 mL/min) (*anti*-**11a**) t_R = 11.1 min, (*syn*-**11a**) t_R = 12.1 min.

2-(6-Methyl-3(*E*)-hepten-2-yl)-6-methoxy-1,2,3,4-tetrahydronaphthalen-1-one (11b): IR (neat) 2900, 1660, 1595, 1440, 1325, 1240, 1020, and 960 cm^{-1}; ^1H NMR (90 MHz) (*anti*-**11b**) δ 0.84 (d, 6H, J = 6.6 Hz), 0.95 (d, 3H, J = 7.2 Hz), 1.3−2.2 (m, 5H), 2.4−3.4 (m, 4H), 3.83 (s, 3H), 5.2−5.6 (m, 2H), 6.6−6.8 (m, 2H), 8.00 (d, 1H, J = 8.7 Hz), (*syn*-**11b**) δ 0.80 (d, 3H, J = 6.6 Hz), 1.04 (d, 3H, J = 7.2 Hz), 1.2−2.2 (m, 5H), 2.4−3.0 (m, 4H), 3.83 (s, 3H), 5.1−5.5 (m, 2H), 6.6−6.8 (m, 2H), 8.00 (d, 1H, J = 8.7 Hz); HPLC (Zorbax SIL, hexane:ethyl acetate = 19:1, flow rate 1.2 mL/min) (*anti*-**11b**) t_R = 11.6 min, (*syn*-**11b**) t_R = 12.9 min.

2-(3-Buten-2-yl)cyclopentanone (12a): IR (neat) 2900, 1710, 1400, 1150, and 910 cm^{-1}; ^1H NMR (90 MHz) (*anti*-**12a**) δ 0.99 (d, 3H, J = 6.9 Hz), 1.3−2.1 (m, 8H), 4.9−5.1 (m, 2H), 5.82 (ddd, 1H, J = 18.9, 9.6, 6.6 Hz), (*syn*-**12a**) δ 1.10 (d, 3H, J = 6.6 Hz), 1.2−2.3 (m, 8H), 4.9−5.2 (m, 2H), 5.66 (ddd, 1H, J = 17.4, 10.4, 7.5 Hz); HPLC (Zorbax SIL, hexane:ethyl acetate = 60:1, flow rate 1.0 mL/min) (*anti*-**12a**) t_R = 17.7 min, (*syn*-**12a**) t_R = 18.1 min.

2-(3(*E*)-Penten-2-yl)cyclopentanone (12c): IR (neat) 2900, 1700, 1460, 1190, 960, and 855 cm^{-1}; ^1H NMR (90 MHz) (*anti*-**12c**) δ 0.93 (d, 3H, J = 6.9 Hz), 1.5−2.8 (m, 11H), 5.2−5.6 (m, 2H), (*syn*-**12c**) δ 1.07 (d, 3H, J = 7.2 Hz), 1.63 (d, 3H, J = 5.4 Hz) 1.3- 2.7 (m, 8H), 5.2−5.7 (m, 2H); HPLC (Zorbax SIL, hexane:ethyl acetate = 60:1, flow rate 1.0 mL/min) (*anti*-**12c**) t_R = 15.9 min, (*syn*-**12c**) t_R = 16.7 min.

Palladium-Catalyzed Claisen Rearrangement of 1-(Crotyloxy)-1-cyclopentene: Synthesis of 2-(3-Buten-2-yl)cyclopentanone (12a). To a solution of $PdCl_2(MeCN)_2$ (13 mg, 0.05 mmol) in toluene (1 mL) was added a solution of 1-(crotyloxy)-1-cyclopentanone (70 mg, 0.5 mmol) in toluene (2 mL) at room temperature under an argon atmosphere. After stirring at that temperature for 20 h, the resulting mixture was filtered through Florisil. Removal of the solvent followed by column chromatography on silica gel gave **12a** (55 mg, 78%).

Synthesis of 6-Methyl-5-octa-7-enolide 13a. To a mixture of **12a** (276 mg, 2 mmol) and sodium acetate (1.4 g, 17 mmol) in dichloromethane was added 40% peracetic acid (4.5 mL, 4.5 mmol) at −78 °C. The mixture was warmed to room temperature over 36 h (monitored by TLC) and then poured into saturated sodium bicarbonate solution. The layers were separated, and the aqueous layer was extracted with dichloromethane. The combined organic layers were washed with water and dried over magesium sulfate. Removal of the solvent followed by column chromatography afforded the lactone **13a** (203 mg, 66%): IR (neat) 2990, 1715, 1380, 1240, 1175, 1055, 915, and 735 cm^{-1}; ^1H NMR (90 MHz) (*anti*-**13a**) δ 1.11 (d, 3H, J = 8.4 Hz), 1.3−2.7 (m, 7H), 4.24 (m, 1H), 4.9−5.2 (m, 2H), 5.83 (ddd, 1H, J = 18.0, 9.7, 7.5 Hz), (*syn*-**13a**) δ 1.13 (d, 3H, J = 8.1 Hz), 1.2−2.6 (m, 7H), 4.14 (m, 1H), 5.0−5.3 (m, 2H), 5.70 (ddd, 1H, J = 18.0, 10.5, 7.8 Hz); ^{13}C NMR (*anti*-**13a**) δ 171.6, 138.5, 116.2, 83.4, 42.3, 29.6, 24.8, 18.5, and 15.5, (*syn*-**13a**) δ 171.5, 139.0, 116.0, 83.5, 42.9, 29.7, 25.4, 18.6, and 15.5; HPLC (Zorbax SIL, hexane:ethyl acetate = 60:1, flow rate 1.0 mL/min) (*anti*-**13a**) t_R = 17.7 min, (*syn*-**13a**) t_R = 18.1 min.

Synthesis of 6-Methyl-5-octa-7-enolide 13b. The titled compound was synthesized by the above procedure: IR (neat) 2950, 1715, 1450, 1390, 1240, 1170, 1045, and 915 cm^{-1}; ^1H NMR (500 MHz) (*anti*-**13b**) δ 1.08 (d, 3H, J = 7.0 Hz), 1.68 (dd, 3H, J = 6.4, 1.5 Hz), 1.4−2.0 (m, 4H), 2.4−2.7 (m, 3H), 4.19 (ddd, 1H, J = 11.6, 4.0, 3.0 Hz), 5.35−5.42 (m, 1H), 5.45−5.6 (m, 1H), (*syn*-**13b**) δ 1.09 (d, 3H, J = 6.7 Hz), 1.67 (dd, 3H, J = 6.4, 1.5 Hz), 1.4−2.0 (m, 4H), 2.3−2.7 (m, 3H), 4.07 (ddd, 1H, J = 11.1, 6.7, 2.9 Hz), 5.34 (ddq, 1H, J = 15.3, 7.9, 1.5 Hz), 5.53 (dqd, 1H, J = 15.3, 6.4, 0.6 Hz); ^{13}C NMR (*anti*-**13b**) δ 171.5, 131.4, 126.9, 83.8, 41.5, 29.7, 25.0, 18.8, 17.8, and 16.1, ^{13}C NMR (*syn*-**13b**) δ 171.4, 131.9, 126.7, 84.0, 42.0, 29.6, 25.5, 18.6, 17.8, and 16.1; HPLC (Zorbax SIL, hexane:ethyl acetate = 60:1, flow rate 1.0 mL/min) (*anti*-**13b**) t_R = 15.9 min, (*syn*-**13b**) t_R = 16.7 min.

Preparation of the Methyl Ketone 14 from (*R*)-Glyceraldehyde Acetonide 5. To a stirred solution of methylmagnesium iodide (100 mmol) in ether (70 mL) was slowly added a solution of glyceraldehyde **5** (11.7 g, 70 mmol) in ether (30 mL) at 0 °C under argon atmosphere, and the resulting mixture was stirred for 3 h at that temperature. The reaction mixture was poured into ice−water and neutralized with 1 N HCl. The layers were separated, and the aqueous layer was extracted with ether. The combined extracts were washed with brine and dried over magnesium sulfate. Removal of the solvent afforded crude alcohol, which was used for the next oxidation step without purification.

To a solution of oxalyl chloride (7.3 mL, 83 mmol) in dichloromethane (120 mL) was slowly added a solution of dimethyl sulfoxide (11.7 mL, 165 mmol) in dichloromethane (15 mL) at −60 °C under an argon atmosphere (exothermic gas evolution). After stirring for 20 min at that temperature, a solution of the alcohol (4.4 g, 30 mmol) in dichloromethane (15 mL) was added. Stirring was continued for 20 min before triethylamine (52 mL, 375 mmol) was added, keeping the temperature below −40 °C. After 10 min the reaction mixture was warmed to room temperature and 30 min later poured into water. The layers were separated, and the aqueous layer was extracted with dichloromethane. The combined extracts were washed with 1.5 N HCl and saturated sodium bicarbonate solution and dried over magnesium sulfate. Removal of the solvent afforded crude methyl ketone **14**, which was used for the next reaction without further purification. Analytically pure product was purified by fractional distillation to give the titled compound: bp 55−56 °C (12 mmHg); $[\alpha]^{26}_D$ +74.1° (*c* 1.60, $CHCl_3$) [lit.[25] $[\alpha]^{20}_D$ +53.3°]; ^1H NMR δ 1.40 and 1.50 (2s, 6H), 2.26 (s, 3H), 4.00 (dd, 1H, J = 6.0, 8.4 Hz), 4.25 (dd, 1H, J = 8.4, 7.2 Hz), 4.47 (dd, 1H, J = 7.2, 6.0 Hz); IR (neat) 3000, 1710, 1380, 1220, 1070, and 850 cm^{-1}.

Preparation of 2,2-Dimethyl-4(*S*)-(hepta-6-yn-2(*Z*)-en-2-yl)-1,3-dioxolane (15b). To a suspension of [5-(trimethylsilyl)-4-pentynyl]-phosphonium bromide (19.2 g, 40 mmol) in THF (100 mL) was added a 1.6 N hexane solution of *n*-BuLi (25 mL, 40 mmol) at 0 °C under argon atmosphere. After stirring for 30 min at that temperature, a solution of the methyl ketone **14** (30 mmol) in THF (20 mL) was slowly

added dropwise at −78 °C. After stirring for 3 h at that temperature, the mixture was slowly warmed to room temperature. To the mixture was added hexane (200 mL), and the precipitate was removed by filtration on Celite. Removal of the solvent yielded the crude Wittig product **15a** (R = $SiMe_3$), which was used for the next deprotection step directly.

To a solution of the Wittig product in THF (30 mL) was added a 1 N THF solution of *n*-BuN_4F (30 mL, 30 mmol) at room temperature. After the reaction completed, the reaction mixture was poured into water. The mixture was extracted with ethyl acetate, washed with brine, and dried over magnesium sulfate. Removal of the solvent gave desilylated product **15b** (R = H). Analytically pure sample was purified by fractional distillation (65−67 °C (2 mmHg)) to afford the titled compound **15b**: $[\alpha]^{28}_D$ +0.16° (*c* 1.68, $CHCl_3$); ^1H NMR (200 MHz) δ 1.37 and 1.45 (2s, 6H), 1.74 (br s, 3H), 1.96 (t, 1H, J = 1.5 Hz), 2.0−2.4 (m, 4H), 3.61 (t, 1H, J = 8.1 Hz), 4.02 (dd, 1H, J = 8.1, 7.5 Hz), 4.97 (dd, 1H, J = 8.1, 7.5 Hz), 5.3−5.6 (m, 1H); ^{13}C NMR δ 133.8, 127.5, 109.2, 83.8, 73.8, 68.8, 67.7, 26.6, 26.4, 25.6, 19.1, and 17.9; IR (neat) 3300, 2950, 2100, 1450, 1380, 1245, 1210, 1160, 1060, 860, and 650 cm^{-1}; MS *m/e* 179 (M^+ − 15(CH_3)), 136 (M^+ − 58(CH_3COCH_3)).

Preparation of Methyl 8(*S*)-Hydroxy-7-methyl-9-[(thexyldimethylsilyl)oxy]nona-2-yn-6(*Z*)-enoate ((*S*,*Z*)-3). To a solution of **15b** (4.47 g, 23 mmol) in THF (50 mL) was added a 1.6 N hexane solution of *n*-BuLi at −78 °C under an argon atmosphere. After stirring for 30 min at that temperature, methyl chloroformate (3.1 mL, 40 mmol) was added all at once. After the mixture was slowly warmed to room temperature, it was poured into water. The resultant mixture was extracted with ethyl acetate, washed with saturated ammonium chloride solution and brine, and dried over magnesium sulfate. Removal of the solvent gave the methoxycarbonyl compound **15c** (R = CO_2Me), which was used for the next reaction without purification.

A solution of **15c** (30 mL, crude) and a catalytic amount of *p*-toluenesulfonic acid in methanol (50 mL) were stirred for 2 days at room temperature. Two-thirds of the solvent was removed and diluted with ether. The solution was neutralized with saturated sodium bicarbonate solution, washed with brine, and dried over magnesium sulfate. Removal of the solvent afforded the diol **3a**, which was used for the next silylation step.

To a solution of imidazole (0.68 g, 10 mmol) in DMF (5 mL) was added a solution of thexyldimethylsilyl chloride (1.97 g, 11 mmol) in DMF (5 mL) at 0 °C under a nitrogen atmosphere. After stirring for 30 min, the reaction vessel was cooled to −40 °C. To this mixture was added a solution of the diol (2.12 g, 10 mmol) in DMF (10 mL). After stirring for 4 h at that temperature, the reaction mixture was poured into water. The mixture was extracted with ethyl acetate three times, and the combined extracts were washed with water four times. Then the extract was washed with brine and dried over magnesium sulfate. Removal of the solvent followed by column chromatography on silica gel gave the titled allyl alcohol **3b** (3.16 g, 86% from **5**): $[\alpha]^{24}_D$ +23.9° (*c* 2.01, $CHCl_3$); ^1H NMR (90 MHz) δ 0.10 (s, 6H), 0.80 (s, 6H), 0.88 (s, 6H), 1.5−1.8 (m, 1H), 1.70 (br s, 3H), 2.0−2.4 (m, 4H), 3.49 (d, 2H, J = 8.1 Hz), 3.80 (s, 3H), 4.52 (t, 1H, J = 8.1 Hz), 5.2−5.4 (m, 1H); ^{13}C NMR δ 154.0, 136.5, 125.5, 89.0, 73.1, 70.4, 65.2, 52.4, 34.2, 25.6, 25.2, 20.3, 19.8, 18.5, and 3.5; IR (neat) 3400, 2950, 2220, 1700, 1460, 1430, 1260, 1100, 1060, 840, and 770 cm^{-1}; MS *m/e* 337 (M^+ − 17(OH)), 293 (M^+ − 61(CO_2CH_3)).

Tandem Claisen−Ene Reaction of 3 and 4: Synthesis of 1-((*E*)-Carbomethoxymethylene)-2-(formylmethyl)-3-(6-methoxy-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)-2-methylcyclopentane (2). A solution of **3b** (177 mg, 0.5 mmol), the enol ether **4**, and DMP (6.1 mg, 0.05 mmol) in toluene was heated at 180 °C for 60 h in a sealed tube under a nitrogen atmosphere. After the reaction mixture was concentrated under reduced pressure, THF (30 mL) and 3 N HCl (5 mL) were added. The mixture was stirred for 10 h at 30 °C. The mixture was neutralized with saturated sodium bicarbonate solution, washed with brine, and dried over magnesium sulfate. Removal of the solvent followed by column chromatography on silica gel afforded a diastereomeric mixture of the ketoaldehyde **2**. Data for 8,14-*syn*-13,14-*trans*-**2**: $[\alpha]^{19}_D$ +77.1° (*c* 2.31, $CHCl_3$); mp 129 °C; ^1H NMR (500 MHz) δ 1.16 (s, 3H), 1.6−1.8 (m, 2H), 2.0−2.4 (m, 3H), 2.5−3.0 (m, 6H) 3.2−3.3 (m, 1H), 3.69 (s, 3H), 3.85 (s, 3H), 5.73 (t, 1H, J = 2.5 Hz), 6.67 (d, 1H, J = 2.2 Hz), 6.82 (dd, 1H, J = 8.9, 2.4 Hz), 7.95 (d, 1H, J = 8.9 Hz), 9.70 (t, 1H, J = 1.2 Hz); ^{13}C NMR δ 201.4, 197.8, 174.1, 167.0, 163.6, 145.6, 130.0, 126.2, 113.5, 112.4, 111.3, 55.4, 53.3, 51.0, 48.8, 47.7, 44.3, 31.6, 27.9, 27.4, 26.8, and 23.4; IR ($CHCl_3$) 2900, 1700, 1660, 1590, 1490, 1450, 1430, 1350, 1300−1160, 1020, and 970 cm^{-1}. Anal. Calcd for $C_{22}H_{26}O_5$: C, 71.33; H, 7.07. Found: C, 71.03; H, 7.14. Data for 8,14-*anti*-13,14-*trans*-**2**: ^1H NMR (90 MHz) δ 1.16 (s, 3H), 1.6−3.3 (m, 12H), 3.69 (s, 3H), 3.85 (s, 3H), 5.65 (m, 1H), 6.67 (d, 1H, J = 2.5 Hz), 6.82 (dd, 1H, J = 8.8, 2.5 Hz), 7.95 (d, 1H, J = 8.8 Hz), 9.45 (m, 1H)

Ozonolysis of the Claisen−Ene Product 2: 2-(Formylmethyl)-3-(6-methoxy-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)-2-methylcyclopentanone (16, Ziegler's Diketoaldehyde). A stream of ozone was bubbled into a suspension of the mixture of **2** (276 mg, 0.74 mmol) in methanol (15 mL) at −35 °C for 10 min till the suspension turned to a clear solution. To this solution was added dimethyl sulfide (0.5 mL) at that temperature, and the resultant mixture was warmed to room temperature. After stirring for 3 h, solvent was removed, which followed by column chromatography on silica gel yielded the diastereomeric mixture of **16** (157 mg, 67%). Data for 8,14-*syn*-**16**: ^1H NMR (90 MHz) δ 1.06 (s, 3H), 1.2−3.0 (m, 12H), 3.90 (s, 3H), 6.6−6.9 (m, 2H), 8.00 (d, 1H, J = 8.9 Hz), 9.76 (br s, 1H). Data for 8,14-*anti*-**16**: $[\alpha]^{23}_D$ −0.48° (*c* 0.91, $CHCl_3$); ^1H NMR (500 MHz) δ 1.06 (s, 3H), 1.5−1.7 (m, 2H), 2.0−3.2 (m, 8H), 2.77 (d, 2H, J = 14.1 Hz), 3.84 (s, 3H), 6.66 (d, 1H, J = 2.1 Hz), 6.81 (dd, 1H, J = 8.5, 2.1 Hz), 7.92 (d, 1H, J = 8.5 Hz), 9.35 (s, 1H); IR ($CHCl_3$) 2900, 1725, 1710, 1660, 1590, 1260, and 730 cm^{-1}.

Isomerization of the Diketoaldehyde 8,14-*syn*-16 to 8,14-*anti*-16. To a solution of the diastereomeric mixture **16** was added a catalytic amount of sodium methoxide. The mixture was stirred for 4 h at room temperature. Two-thirds of the solvent was removed under reduced pressure, and the residue was diluted with ethyl acetate. The mixture was washed with saturated ammonium chloride solution and brine and dried over magnesium sulfate. Removal of the solvent followed by short path column chromatography gave the diketoaldehyde *anti*-**16** (69%).

Synthesis of 9(11)-Dehydroestrone Methyl Ether (1). A suspension of $TiCl_3$ (230 mg, 1.5 mmol) and zinc−silver couple (193 mg, 3 mmol based on silver) in DME was refluxed for 2 h under an argon atmosphere (color of the suspension turned to green). To this reaction mixture was added a solution of the diketoaldehyde *anti*-**16** (93 mg, 0.3 mmol) in DME (5 mL). The reaction mixture was refluxed for 2 h. Upon cooling to room temperature, the reaction mixture was passed through Florisil, and the Florisil was washed with ethyl acetate. Removal of the solvent followed by column chromatography on silica gel yielded the titled compound **1** (31 mg, 56%): $[\alpha]^{21}_D$ +258° (*c* 0.70, $CHCl_3$) [lit.[4a] $[\alpha]^{25}_D$ +247.2° (>97.3% ee) (*c* 0.50, $CHCl_3$)]; ^1H NMR (500 MHz) δ 0.94 (s, 3H), 1.4−1.8 (m, 4H), 2.2−3.0 (m, 8H), 3.79 (s, 3H), 6.13 (t, 1H, J = 2.8 Hz), 6.61 (d, 1H, J = 2.8 Hz), 6.73 (dd, 1H, J = 8.6, 2.8 Hz), 7.53 (d, 1H, J = 8.6 Hz); IR ($CHCl_3$) 2900, 1725, 1600, 1490, 1210, and 720 cm^{-1}; HRMS *m/z* calcd for $C_{19}H_{22}O_2$ 282.1621, found 282.1648.

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