Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron
Tetrahedron 63 (2007) 12639–12645

Sequential pericyclic reaction of ene-diallene: synthesis of (±)-estrone

Hirohumi Hakuba, Shinji Kitagaki* and Chisato Mukai*

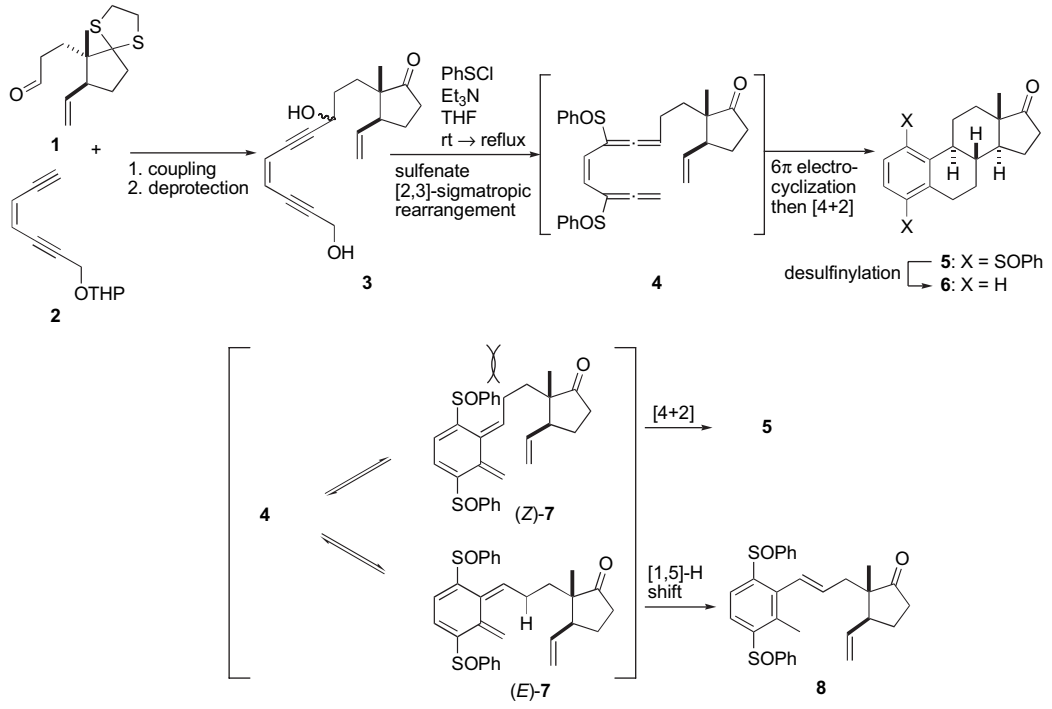
Division of Pharmaceutical Sciences, Graduate School of Natural Science and Technology, Kanazawa University, Kakuma-machi, Kanazawa 920-1192, Japan

Received 11 September 2007; revised 1 October 2007; accepted 2 October 2007
Available online 6 October 2007

Abstract—The one-pot construction of perhydrophenanthrene from an acyclic substrate was achieved via a sequential pericyclic reaction, which involved the in situ generation of ene-diallene species due to Myers' propargyl alcohol–allene transformation. The resulting perhydrophenanthrene derivative could be successfully converted into (±)-estrone.

1. Introduction

The development of a novel and efficient tandem reaction is currently the central issue for the synthesis of structurally complex molecules. The one-pot construction of polycyclic compounds from acyclic precursors is one of the most challenging synthetic reactions. We recently reported the convenient synthesis of estra-1,3,5(10)-trien-17-one (**6**) based on the sequential pericyclic reaction triggered by the in situ generation of ene-bis(sulfinylallene) species (Scheme 1).[1] Thus, the consecutive sequences, which totally involve the sulfenic ester formation from bis(propargyl alcohol) **3**,



Scheme 1.

Keywords: Allenes; Tandem reaction; [4+2] Cycloaddition; Estrone.
* Corresponding authors. Tel.: +81 76 234 4411; fax: +81 76 234 4410; e-mail addresses: kitagaki@p.kanazawa-u.ac.jp; cmukai@kenroku.kanazawa-u.ac.jp

0040–4020/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2007.10.008

easily prepared from an aldehyde **1** and enediyne **2**, using benzenesulfenyl chloride (PhSCl) (first step), dual [2,3]-sigmatropic rearrangement of the ester (second step),[2,3] 6π electrocyclic reaction of the ene-diallene **4** (third step),[4] and finally the intramolecular [4+2] cycloaddition of *o*-quinodimethane (*Z*)-**7** (fourth step),[5] enabled the one-pot stereoselective construction of the steroidal compound **5** from the acyclic substrate. However, the total yield of **6** from **3** involving a desulfinylation step (**5** to **6**) was poor (32% yield). Furthermore, it turned out that the substrates, which have simpler structures than **3**, again underwent the above mentioned tandem reaction via the intramolecular [4+2] cycloaddition to give the corresponding cycloadducts in rather low yields. Interestingly, satisfactory yields could be obtained when the in situ generated ene-bis(sulfinyl-allene) species (e.g., **4** without the terminal olefin moiety) was trapped by the external dienophiles (intermolecular [4+2] cycloaddition).[6,7] Thus, these observations indicated that the moderate yields of the cycloadducts in the above mentioned tandem reaction via the intramolecular [4+2] cycloaddition might be attributed to the nonbonding interaction between the phenylsulfinyl group and the methylene tether of (*Z*)-**7**, an essential intermediate for the intramolecular cycloaddition. This would not be the case for the alternative intermediate (*E*)-**7** in which the methylene tether is oriented opposite to the phenylsulfinyl group, although another unfavorable interaction between the *exo*-methylene protons and the allylic hydrogens might occur. Indeed, the sufficient amounts of product **8**, which must have been produced via the [1,5] hydrogen-shift of the intermediate (*E*)-**7**, were detected.[8] Thus, we envisaged that the generation of the ene-diallene species without the phenylsulfinyl group would make the intramolecular [4+2] cycloaddition process (fourth step) to occur more easily. We now report the in situ generation of the unfunctionalized ene-diallene species[4c,d,f–j] and its application to the total synthesis of the racemic estrone.

2. Results and discussion

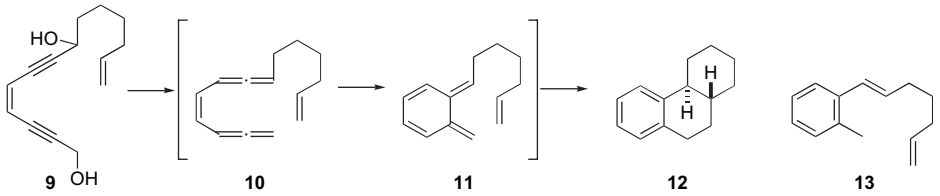
2.1. Pericyclic reaction via generation of unfunctionalized ene-diallene by Myers' allene forming reaction

The bis(propargyl alcohol) **9**[1] was selected for the initial evaluation of the in situ generation of the unfunctionalized ene-diallene derivative using the Myers' propargyl alcohol–allene transformation protocol[9] (Table 1). *o*-Nitrobenzenesulfonylhydrazine (NBSH) was added to a solution of triphenylphosphine, diethyl azodicarboxylate (DEAD), and **9** in THF at −15 °C. The resulting mixture was kept at the same temperature for 1 h and then at room temperature for 1 h. Further stirring at 50 °C for 1 h resulted in the production of the perhydrophenanthrene **12** in an unexpectedly low yield (20%) (entry 1). The highest yield (62%) was observed when the reaction mixture was kept at 50 °C for 15 h (entry 2). On the other hand, the refluxing temperature led to a decrease in the yield (entry 3). Tosylhydrazine, used instead of NBSH, resulted in the production of **12** in 52% yield (entry 4). A similar result was obtained using *N*-isopropylidene-*N*′-*o*-nitrobenzenesulfonylhydrazine (IPNBSH), which was recently reported as an alternative to NBSH by Movassaghi and Ahmad (entry 5).[10] It should be stated that no [1,5] hydrogen-shifted product **13** was detected in all the reactions. The present method is obviously preferred over the previously developed one (entry 6)[1] from the viewpoint of the chemical yield as well as the much simpler operation.

2.2. Total synthesis of racemic estrone

Encouraged by the improvement in the chemical yield of **12**, we embarked on the synthesis of the racemic estrone[11] based on the newly developed method. Preparation of the cyclopentane derivative, the D-ring unit of estrone having a dienophile part, commenced with the stereoselective

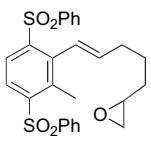
Table 1. Sequential reaction of bis(propargyl alcohol) **9**



9 **10** **11** **12** **13**

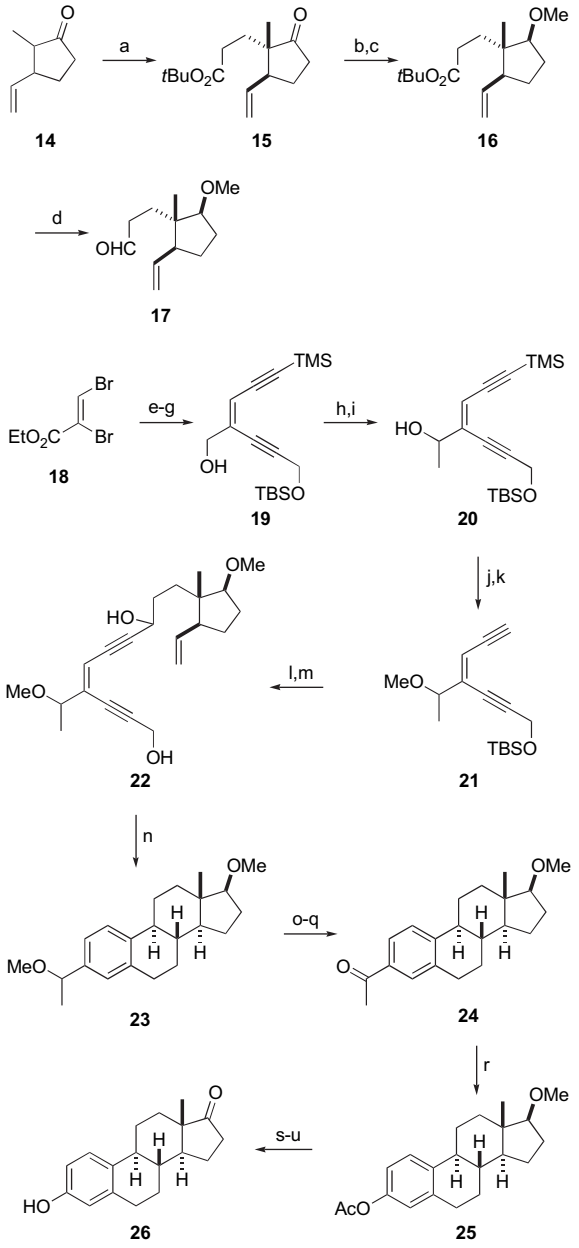
Entry	Conditions	Yield of **12** (%)	Yield of **13** (%)
1	PPh_3 (5 equiv), DEAD (5 equiv), *o*-$NO_2C_6H_4SO_2NHNH_2$ (NBSH) (5 equiv), THF, −15 °C→rt→50 °C[a]	20	—
2	PPh_3 (5 equiv), DEAD (5 equiv), NBSH (5 equiv), THF, −15 °C→rt→50 °C[b]	62	—
3	PPh_3 (5 equiv), DEAD (5 equiv), NBSH (5 equiv), THF, −15 °C→rt→reflux	46	—
4	PPh_3 (5 equiv), DEAD (5 equiv), $TsNHNH_2$ (5 equiv), benzene, 5 °C→rt then MeOH, reflux	52	—
5	PPh_3 (5 equiv), DEAD (5 equiv), *o*-$NO_2C_6H_4SO_2NHN{=}C(CH_3)_2$ (IPNBSH) (5 equiv), THF, rt then TFE–H_2O (1:1), 50 °C	48	—
6	(1) PhSCl (6 equiv), Et_3N, (7 equiv), THF, rt→reflux (2) *m*-CPBA, CH_2Cl_2 (3) Mg, MeOH, 50 °C	46	33[c]

[a] Reaction performed for 1 h at 50 °C.
[b] Reaction performed for 15 h at 50 °C.
[c] Yield of **13′** obtained by *m*-CPBA oxidation after sequential pericyclic reaction.



13′

introduction of the C_3-unit (*t*-butyl acrylate) to the known 2-methyl-3-vinylcyclopentanone (**14**)[12] to produce **15** in 66% yield (Scheme 2).[13] Stereoselective reduction of the ketone carbonyl group of **15** with sodium borohydride,[14] and methylation of the resulting alcohol was followed by reduction of the ester functionality with DIBAL-H to afford the aldehyde **17**.



Scheme 2. Reagents and conditions: (a) *t*-BuOK, $CH_2{=}CHCO_2t$-Bu, THF (66%); (b) $NaBH_4$, MeOH; (c) 2,6-di-*t*-butylpyridine, MeOTf, CH_2Cl_2 (60% from **15**); (d) DIBAL-H, toluene, −78 °C (70%); (e) HC≡CTMS, $Pd(PPh_3)_4$, CuI, *i*-Pr_2NEt, DMF; (f) DIBAL-H, toluene, −78 °C; (g) HC≡CCH_2OTBS, $Pd(PPh_3)_4$, CuI, *n*-$BuNH_2$, benzene, 50 °C (40% from **18**); (h) Dess–Martin periodinane, CH_2Cl_2; (i) MeLi, Et_2O, −78 °C (51% from **19**); (j) NaH, MeI, THF, 0→50 °C; (k) K_2CO_3, MeOH, 0 °C→rt (71% from **20**); (l) *n*-BuLi, **17**, THF, −78 °C; (m) TBAF, THF, 0 °C (61% from **21**); (n) PPh_3, DEAD, IPNBSH, THF, rt then TFE–H_2O (1:1), 50 °C (38%); (o) HNO_3, CH_2Cl_2; (p) NaOH, THF–H_2O, 50 °C; (q) Dess–Martin periodinane, CH_2Cl_2 (72% from **23**); (r) *m*-CPBA, $Sc(OTf)_3$, CH_2Cl_2 (64%); (s) $AlBr_3$, EtSH; (t) CrO_3, H_2SO_4, acetone; (u) K_2CO_3, MeOH (89% from **25**).

The synthesis of the enediyne unit **21** was performed as follows. The successive Sonogashira reaction of the known ethyl (*Z*)-dibromopropenoate (**18**),[15] reduction, and the Sonogashira reaction furnished the enediynol **19**. Dess–Martin oxidation and subsequent addition of methyllithium to the resulting aldehyde furnished the secondary alcohol **20**, which was subsequently converted into **21** by protection of the hydroxy group with methyl iodide and removal of the terminal trimethylsilyl group. The coupling reaction of these two components **17** and **21** was realized by the addition of the acetylide, derived from **21**, to the aldehyde **17** to provide, after desilylation, the ene-bis(propargyl alcohol) **22** as an inseparable mixture of diastereoisomers.[16]

With the substrate for the sequential pericyclic reaction in hand, the aforementioned procedures for the preparation of **12** were examined. As a result, Movassaghi's protocol showed the best result for the transformation of **22** into **23**. Thus, the treatment with IPNBSH under Mitsunobu conditions and subsequent exposure to TFE–H_2O at 50 °C furnished the desired polycyclic compound **23** as an inseparable mixture of two diastereomers in 38% yield.[17] The selective demethylation of the benzyl alcohol moiety using nitric acid[18] and Dess–Martin oxidation produced the methyl ketone **24**, which was exposed to *m*-CPBA in the presence of scandium triflate to afford the acetate **25**.[19,20] Deprotection of the hydroxyl group on the D-ring was followed by the consecutive Jones' oxidation and deacetylation to provide the (±)-estrone (**26**).

3. Conclusion

We have shown that Myers' propargyl alcohol–allene transformation protocol could be applicable to the sequential reaction of ene-bis(propargyl alcohols) leading to polycyclic compounds, and our method effected the total synthesis of (±)-estrone. The present method would provide a new synthesis route for the (+)-estrone, because some enantioselective syntheses of (3*S*)-2-methyl-3-vinylcyclopentanone and its related compounds (D-ring unit) have already been reported.[21]

4. Experimental

4.1. General

Melting points are uncorrected. IR spectra were measured in $CHCl_3$. ^1H NMR and ^{13}C NMR spectra were recorded on a 500 MHz spectrometer. ^1H NMR spectra were taken in $CDCl_3$. $CHCl_3$ (7.26 ppm) for silyl compounds and tetramethylsilane (0.00 ppm) for compounds without a silyl group were used as internal standards. ^{13}C NMR spectra were recorded in $CDCl_3$ with $CDCl_3$ (77.00 ppm) as an internal standard. All reactions were carried out under a nitrogen atmosphere. Silica gel (silica gel 60, 230–400 mesh) was used for chromatography. Organic extracts were dried over anhydrous Na_2SO_4.

4.2. Sequential pericyclic reaction of ene-bis(propargyl alcohol) 9

4.2.1. Sequential pericyclic reaction with NBSH (Table 1, entry 2). To a solution of PPh_3 (156 mg, 0.596 mmol) in

THF (3.0 mL) was added 40% DEAD in toluene (0.30 mL, 0.60 mmol) at −15 °C, and the mixture was stirred for 10 min at that temperature. A solution of bis(propargyl alcohol) **9** (26.0 mg, 0.119 mmol) in THF (5.0 mL) was added to the mixture, which was stirred for 2.5 h at −15 °C. A solution of NBSH (129 mg, 0.596 mmol) was added, and the mixture was stirred for 10 h at −15 °C, 1 h at rt, and then for 15 h at 50 °C. The reaction was quenched by addition of water, and the mixture was extracted with AcOEt. The extract was washed with water and brine, dried, and concentrated to dryness. Chromatography of the residue with hexane gave perhydrophenanthrene (13.5 mg, 62%) as a colorless oil.

4.2.2. Sequential pericyclic reaction with tosylhydrazine (Table 1, entry 4). To a solution of bis(propargyl alcohol) **9** (20.9 mg, 0.096 mmol) in benzene (1.0 mL) were successively added PPh_3 (126 mg, 0.479 mmol), 40% DEAD in toluene (0.24 mL, 0.48 mmol), and tosylhydrazine (89.2 mg, 0.479 mmol) at 5 °C. After being stirred for 1 h at that temperature, the mixture was concentrated to dryness. The residue was taken up to MeOH (5.0 mL) and refluxed for 3 h. After cooling, the reaction mixture was diluted with water and extracted with AcOEt. The extract was washed with water and brine, dried, and concentrated to dryness. Chromatography of the residue with hexane gave perhydrophenanthrene (9.3 mg, 52%) as a colorless oil.

4.3. Synthesis of estrone

4.3.1. *t*-Butyl 3-[(1*R,5*R**)-1-methyl-2-oxo-5-vinylcyclopentyl]propanoate (15).** To a solution of 2-methyl-3-vinylcyclopentanone (745 mg, 6.00 mmol) in THF (12 mL) was added *t*-BuOK (135 mg, 1.20 mmol) at room temperature, and the mixture was stirred for 30 min. A solution of *t*-butyl acrylate (1.14 g, 9.00 mmol) in THF (8 mL) was added and the resulting mixture was stirred for 15 h. The reaction was quenched by addition of saturated aqueous NH_4Cl, and the mixture was extracted with AcOEt. The extract was washed with water and brine, dried, and concentrated to dryness. Chromatography of the residue with hexane–AcOEt (5:1) afforded **15** (986 mg, 66%) as a colorless oil. IR 1724 cm^{-1}; ^1H NMR δ 5.75–5.68 (1H, m), 5.08–5.05 (2H, m), 2.55–2.50 (1H, m), 2.35–2.29 (1H, m), 2.27–1.95 (4H, m), 1.78–1.60 (3H, m), 1.36 (9H, s), 0.79 (3H, s); ^{13}C NMR δ 221.7, 172.6, 136.9, 116.7, 80.1, 50.6, 48.2, 36.8, 30.5, 30.3, 28.0, 24.3, 17.3; MS *m*/*z* 252 (M^+, 38); HRMS calcd for $C_{15}H_{24}O_3$ 252.1726, found 252.1730.

4.3.2. *t*-Butyl 3-[(1*R,2*R**,5*R**)-2-methoxy-1-methyl-5-vinylcyclopentyl]propanoate (16).** To a solution of **15** (181 mg, 0.715 mmol) in MeOH (5.0 mL) was added $NaBH_4$ (135 mg, 3.58 mmol) at −78 °C, and the mixture was stirred for 30 min at that temperature. The reaction was quenched by addition of water, and the mixture was extracted with AcOEt. The extract was washed with water and brine, dried, and concentrated to dryness. The residue was passed through a short pad of silica gel with hexane–AcOEt (3:1) to afford the crude cyclopentanol (182 mg) as a colorless oil. To a solution of the above cyclopentanol (182 mg) in CH_2Cl_2 (5.0 mL) were successively added a solution of 2,6-di-*t*-butylpyridine (682 mg, 3.57 mmol) in CH_2Cl_2 (1.0 mL) and MeOTf (242 μL, 2.14 mmol) at room temperature, and the mixture was refluxed for 12 h. After cooling, the reaction was quenched by addition of 10% aqueous HCl. The organic layer was separated, washed with saturated aqueous $NaHCO_3$, water and brine, dried, and concentrated to dryness. Chromatography of the residue with hexane–AcOEt (10:1) afforded **16** (115 mg, 60% for two steps) as a colorless oil. IR 1720 cm^{-1}; ^1H NMR δ 5.72 (1H, ddd, *J*=16.5, 10.4, 7.9 Hz), 5.00–4.96 (2H, m), 3.34 (1H, t, *J*=7.9 Hz), 3.28 (3H, s), 2.35–2.22 (2H, m), 2.11 (1H, dd, *J*=18.3, 8.5 Hz), 2.04–1.97 (1H, m), 1.72–1.49 (5H, m), 1.43 (9H, s), 0.73 (3H, s); ^{13}C NMR δ 173.9, 138.9, 115.6, 88.3, 79.8, 57.3, 50.7, 45.8, 34.8, 30.7, 28.1, 27.0, 25.8, 12.9; FABMS *m*/*z* 269 (M^++1, 12); HRFABMS calcd for $C_{16}H_{29}O_3$ 269.2117, found 269.2111.

4.3.3. 3-[(1*R,2*R**,5*R**)-2-Methoxy-1-methyl-5-vinylcyclopentyl]propanal (17).** To a solution of **16** (115 mg, 0.430 mmol) in toluene (8.0 mL) was added DIBAL-H in hexane (1.0 M, 0.52 mL, 0.52 mmol) at −78 °C, and the mixture was stirred for 1 h at that temperature. The reaction was quenched by addition of water, and the mixture was diluted with AcOEt, filtered through a short pad of Celite, and concentrated to dryness. Chromatography of the residue with hexane–AcOEt (5:1) afforded **17** (59 mg, 70%) as a colorless oil. IR 1720 cm^{-1}; ^1H NMR δ 9.75 (1H, s), 5.71 (1H, ddd, *J*=17.1, 9.2, 8.5 Hz), 5.01 (1H, d, *J*=9.2 Hz), 4.98 (1H, d, *J*=17.1 Hz), 3.31 (1H, t, *J*=8.6 Hz), 3.25 (3H, s), 2.62–2.55 (1H, m), 2.49–2.46 (1H, m), 2.11 (1H, dd, *J*=10.4, 8.5 Hz), 2.06–1.99 (1H, m), 1.73–1.42 (5H, m), 0.74 (3H, s); ^{13}C NMR δ 203.0, 138.7, 115.9, 88.1, 57.1, 50.9, 45.6, 39.2, 31.5, 26.8, 25.7, 12.7; FABMS *m*/*z* 197 (M^++1, 6.5); HRFABMS calcd for $C_{15}H_{21}O_2$ 197.1542, found 197.1546.

4.3.4. (*E*)-7-(*t*-Butyldimethylsiloxy)-4-hydroxymethyl-1-(trimethylsilyl)hept-3-ene-1,5-diyne (19). To a solution of **18** (2.04 g, 7.91 mmol), trimethylsilylacetylene (1.90 mL, 13.4 mmol), $Pd(PPh_3)_4$ (512 mg, 0.443 mmol), and CuI (301 mg, 1.58 mmol) in DMF (45 mL) was added *i*-Pr_2NEt (2.05 mL, 13.1 mmol) at 0 °C, and the mixture was stirred for 11 h at that temperature. The reaction was quenched by addition of saturated aqueous NH_4Cl, and the mixture was extracted with AcOEt. The extract was washed with water and brine, dried, and concentrated to dryness. The residue was passed through a short pad of silica gel with hexane–AcOEt (10:1) to afford the crude enyne (1.86 g) as a brown oil. To a solution of the above enyne (1.86 g) in toluene (10 mL) was added dropwise DIBAL-H in hexane (1.0 M, 15 mL, 15 mmol) at −78 °C, and the mixture was stirred for 30 min at that temperature and then for 30 min at 0 °C. The reaction was quenched by addition of 10% aqueous HCl, and the mixture was extracted with AcOEt. The extract was washed with water and brine, dried, and concentrated to dryness. The residue was passed through a short pad of silica gel with hexane–AcOEt (7:1) to afford the crude alcohol (930 mg) as a yellow oil. To a solution of the above alcohol (930 mg) in benzene (10 mL) were successively added 3-(*t*-butyldimethylsiloxy)-1-butyne (1.36 g, 7.98 mmol), $Pd(PPh_3)_4$ (231 mg, 0.199 mmol), CuI (152 mg, 0.798 mmol), and *n*-$BuNH_2$ (0.80 mL, 8.0 mmol) at room temperature, and the mixture was stirred for 6 h at 60 °C. After cooling, the reaction was quenched by addition of saturated aqueous NH_4Cl, and the mixture was extracted

with AcOEt. The extract was washed with water and brine, dried, and concentrated to dryness. Chromatography of the residue with hexane–AcOEt (5:1) afforded **19** (1.02 g, 40% for three steps) as a brown oil. IR 3603, 3421, 2133 cm^{-1}; ^1H NMR δ 5.97 (1H, s), 4.52 (2H, s), 4.17 (2H, s), 1.94 (1H, br s), 0.91 (9H, s), 0.20 (9H, s), 0.14 (6H, s); ^{13}C NMR δ 134.8, 114.1, 102.0, 96.8, 81.0, 64.9, 52.2, 25.8, 18.3, −0.1, −5.0; MS *m/z* 322 (M^+, 5.9); HRMS calcd for $C_{17}H_{30}O_2Si_2$ 322.1784, found 322.1788.

4.3.5. (*E*)-7-(*t*-Butyldimethylsiloxy)-4-(1-hydroxyethyl)-1-(trimethylsilyl)hept-3-ene-1,5-diyne (20). To a solution of **19** (567 mg, 1.76 mmol) in CH_2Cl_2 (6.0 mL) was added Dess–Martin periodinane (895 mg, 2.11 mmol) at 0 °C, and the mixture was stirred for 1 h at room temperature. The reaction was quenched by addition of saturated aqueous $Na_2S_2O_3$, and the mixture was extracted with AcOEt. The extract was washed with water and brine, dried, and concentrated to dryness. The residue was passed through a short pad of silica gel with hexane–AcOEt (6:1) to afford the crude aldehyde (400 mg) as a brown oil. To a solution of the above aldehyde (400 mg) in Et_2O (12 mL) was added MeLi in Et_2O (1.0 M, 1.4 mL, 1.4 mmol) at −78 °C, and the mixture was stirred for 10 min at that temperature. The reaction was quenched by addition of saturated aqueous NH_4Cl, and the mixture was extracted with AcOEt. The extract was washed with water and brine, dried, and concentrated to dryness. Chromatography of the residue with hexane–AcOEt (3:1) afforded **20** (299 mg, 51% for two steps) as a brown oil. IR 3587, 2141 cm^{-1}; ^1H NMR δ 5.95 (1H, s), 4.51 (2H, s), 4.29 (1H, q, *J*=6.7 Hz), 2.33 (1H, br s), 1.34 (3H, d, *J*=6.7 Hz), 0.89 (9H, s), 0.18 (9H, s), 0.12 (6H, s); ^{13}C NMR δ 139.6, 113.5, 102.2, 101.8, 97.4, 80.8, 70.0, 52.1, 25.8, 22.5, 18.2, −0.2, −5.1; MS *m/z* 336 (M^+, 6.6); HRMS calcd for $C_{18}H_{32}O_2Si_2$ 336.1941, found 336.1945.

4.3.6. (*E*)-7-(*t*-Butyldimethylsiloxy)-4-(1-methoxyethyl)-hept-3-ene-1,5-diyne (21). To a solution of **20** (299 mg, 0.891 mmol) in THF (8.0 mL) was added NaH (60% in oil, 42.8 mg, 1.1 mmol) at 0 °C, and the mixture was stirred for 5 min at that temperature. MeI (0.11 mL, 1.8 mmol) was added and the resulting mixture was stirred for 12 h at 50 °C. The reaction was quenched by addition of saturated aqueous NH_4Cl, and the mixture was extracted with AcOEt. The extract was washed with water and brine, dried, and concentrated to dryness. The residue was dissolved in MeOH (5.0 mL) and K_2CO_3 (124 mg, 0.900 mmol) was added at 0 °C. After being stirred for 1 h at room temperature, the reaction mixture was diluted with water and extracted with AcOEt. The extract was washed with water and brine, dried, and concentrated to dryness. Chromatography of the residue with hexane–AcOEt (6:1) afforded **21** (213 mg, 71% for two steps) as a brown oil. IR 3304 cm^{-1}; ^1H NMR δ 5.85 (1H, s), 4.52 (2H, s), 3.76 (1H, q, *J*=6.1 Hz), 3.26 (3H, s), 3.24 (1H, d, *J*=2.4 Hz), 1.31 (3H, d, *J*=6.1 Hz), 0.90 (9H, s), 0.13 (6H, s); ^{13}C NMR δ 138.3, 113.4, 97.0, 83.7, 80.7, 79.4, 56.6, 52.2, 25.8, 20.8, 18.2, −5.08, −5.09; MS *m/z* 278 (M^+, 71); HRMS calcd for $C_{16}H_{26}O_2Si$ 278.1702, found 278.1715.

4.3.7. (*E*)-10-[(1*R,2*R**,5*R**)-2-Methoxy-1-methyl-5-vinylcyclopentyl]-4-(1-methoxyethyl)dec-4-ene-2,6-diyne-1,8-diol (22).** To a solution of **21** (106 mg, 0.381 mmol) in THF (2.0 mL) was added *n*-BuLi in hexane (1.56 M, 0.24 mL, 0.38 mmol) at −78 °C, and the mixture was stirred for 1 h at that temperature. A solution of **17** (33.0 mg, 0.168 mmol) was added to the mixture, which was further stirred for 30 min at −78 °C. The reaction was quenched by addition of water, and the mixture was extracted with AcOEt. The extract was washed with water and brine, dried, and concentrated to dryness. The residue was passed through a short pad of silica gel with hexane–AcOEt (3:1) to afford the crude alcohol (50.0 mg) as a yellow oil. To a solution of the above alcohol (50.0 mg) in THF (1.0 mL) was added TBAF in THF (1.0 M, 0.12 mL, 0.12 mmol) at 0 °C. After 1 h, the reaction mixture was diluted with water and extracted with AcOEt. The extract was washed with water and brine, dried, and concentrated to dryness. Chromatography of the residue with hexane–AcOEt (3:2) afforded **22** (36.7 mg, 61% for two steps) as an inseparable mixture of diastereomers in a ratio of ca. 1:1 as a yellow oil. IR 3603, 3400 cm^{-1}; ^1H NMR δ 5.90 (1H, s), 5.73 (1H, ddd, *J*=17.1, 10.4, 8.5 Hz), 5.01 (1H, d, *J*=10.4 Hz), 4.99 (1H, d, *J*=17.1 Hz), 4.51 (1H, dd, *J*=11.0, 4.9 Hz), 4.47 (2H, s), 3.79 (1H, q, *J*=6.1 Hz), 3.42, 3.40 (total 1H, each t, *J*=7.9 Hz), 3.32, 3.31 (total 3H, each s), 3.28 (3H, s), 2.94 (1H, br s), 2.18 (1H, q, *J*=8.6 Hz), 2.05–2.00 (1H, m), 1.84–1.42 (8H, m), 1.34 (3H, d, *J*=6.1 Hz), 0.77 (3H, s); ^{13}C NMR δ 139.1, 139.0, 136.5, 136.4, 115.6, 115.5, 115.0, 114.9, 97.5, 97.4, 96.7, 96.6, 87.8, 87.6, 82.12, 82.11, 81.7, 81.6, 79.4, 63.7, 63.6, 57.4, 57.3, 56.6, 51.4, 51.3, 49.9, 49.7, 49.6, 45.9, 34.4, 34.2, 32.4, 26.9, 26.8, 25.7, 25.6, 20.8, 13.7, 13.6; MS *m/z* 360 (M^+, 7.5); HRMS calcd for $C_{22}H_{32}O_4$ 360.2301, found 360.2314.

4.3.8. 17-Methoxy-3-(1-methoxyethyl)estra-1,3,5(10)-triene (23). To a solution of **22** (13.0 mg, 3.60×10^{-2} mmol) in THF (0.4 mL) were successively added PPh_3 (94.4 mg, 0.360 mmol), IPNBSH (92.6 mg, 0.360 mmol), and DEAD in 40% toluene (0.16 mL, 0.36 mmol) at 0 °C. After 5 min, the reaction mixture was allowed to warm to room temperature. After 3 h, the mixture was diluted with THF (2.0 mL), and TFE–H_2O (1:1, 1.0 mL) was added. After being stirred for 12 h at 50 °C, the reaction mixture was partitioned between hexane and water. The aqueous layer was extracted with hexane, and the combined extracts were washed with water and brine, dried, and concentrated to dryness. Chromatography of the residue with hexane–AcOEt (5:1) afforded **23** (4.5 mg, 38%) as an inseparable mixture of two diastereomers (ratio not determined) as a colorless oil. IR 3007, 2932 cm^{-1}; ^1H NMR δ 7.26–7.24 (1H, m), 7.07–7.04 (1H, m), 6.99 (1H, d, *J*=4.2 Hz), 4.21 (1H, q, *J*=6.4 Hz), 3.36 (3H, s), 3.30 (1H, t, *J*=8.1 Hz), 3.21 (3H, s), 2.86–2.84 (2H, m), 2.32–2.29 (1H, m), 2.25–2.20 (1H, m), 2.06–2.03 (2H, m), 1.89–1.86 (1H, m), 1.72–1.30 (7H, m), 1.41 (3H, d, *J*=6.4 Hz), 1.23–1.17 (1H, m), 0.78 (3H, s); ^{13}C NMR δ 140.6, 139.6, 136.8, 136.7, 126.8, 126.7, 125.4, 125.3, 123.5, 123.4, 90.8, 79.5, 79.4, 57.9, 56.4, 50.5, 44.4, 43.2, 38.4, 38.3, 38.1, 29.6, 29.5, 27.8, 27.2, 26.2, 23.8, 23.7, 23.1, 11.5; MS *m/z* 328 (M^+, 100); HRMS calcd for $C_{22}H_{32}O_2$ 328.2402, found 328.2407.

4.3.9. 3-Acetyl-17-methoxyestra-1,3,5(10)-triene (24). To a solution of **23** (11.3 mg, 3.44×10^{-2} mmol) in CH_2Cl_2 (1.0 mL) was added fuming HNO_3 (14 μL, 0.34 mmol) at 0 °C, and the reaction mixture was stirred for 24 h at room temperature. The mixture was diluted with 10% aqueous

Na_2SO_4 and extracted with AcOEt. The extract was washed with water and brine, dried, and concentrated to dryness. The residue was passed through a short pad of silica gel with hexane–AcOEt (5:1) to afford the crude nitrate (9.5 mg) as a colorless oil. To a solution of the above nitrate (9.5 mg) in THF (1.0 mL) was added 10% aqueous NaOH (1.0 mL) at room temperature. After being stirred for 6 h at 50 °C, the mixture was diluted with water and extracted with AcOEt. The extract was washed with water and brine, dried, and concentrated to dryness. The residue was passed through a short pad of silica gel with hexane–AcOEt (3:1) to afford the crude alcohol (7.9 mg) as a colorless oil. To a solution of the above alcohol (7.9 mg) in CH_2Cl_2 (1.0 mL) was added Dess–Martin periodinane (10.3 mg, 0.184 mmol) at room temperature, and the mixture was stirred for 3 h. The reaction was quenched by addition of saturated aqueous $Na_2S_2O_3$, and the mixture was extracted with AcOEt. The extract was washed with water and brine, dried, and concentrated to dryness. Chromatography of the residue with hexane–AcOEt (5:1) afforded **24** (7.6 mg, 72% for three steps) as colorless needles. Mp 125–127 °C (acetone–hexane); IR 1678 cm^{-1}; ^1H NMR δ 7.70 (1H, d, J=7.9 Hz), 7.65 (1H, s), 7.36 (1H, d, J=7.9 Hz), 3.36 (3H, s), 3.30 (1H, t, J=7.9 Hz), 2.91–2.88 (2H, m), 2.55 (3H, s), 2.33–2.22 (2H, m), 2.08–2.03 (2H, m), 1.92–1.89 (1H, m), 1.69–1.19 (8H, m), 0.78 (3H, s); ^{13}C NMR δ 198.2, 146.2, 137.1, 134.7, 128.9, 125.7, 125.6, 90.7, 57.9, 50.5, 44.7, 43.1, 38.1, 38.0, 29.5, 27.7, 27.0, 26.5, 26.1, 23.1, 11.5; MS m/z 312 (M^+, 100); HRMS calcd for $C_{21}H_{28}O_2$ 312.2089, found 312.2089.

4.3.10. 3-Acetoxyl-17-methoxyestra-1,3,5(10)-triene (25). To a solution of **24** (2.9 mg, 9.3×10^{-3} mmol) in CH_2Cl_2 (1.0 mL) were added *m*-CPBA (7.8 mg, 0.045 mmol) and $Sc(OTf)_3$ (1.0 mg, 2.0×10^{-3} mmol) at room temperature, and the mixture was stirred for 4 days. The reaction was quenched by addition of saturated aqueous $Na_2S_2O_3$, and the mixture was extracted with AcOEt. The extract was washed with water and brine, dried, and concentrated to dryness. Chromatography of the residue with hexane–AcOEt (5:1) afforded **25** (1.9 mg, 64%) as colorless crystals. Mp 70–73 °C (CH_2Cl_2–hexane); IR 1749 cm^{-1}; ^1H NMR δ 7.26 (1H, d, J=8.3 Hz), 6.83 (1H, d, J=8.3 Hz), 6.77 (1H, s), 3.36 (3H, s), 3.30 (1H, t, J=8.1 Hz), 2.84–2.82 (2H, m), 2.28–2.17 (2H, m), 2.05–2.03 (2H, m), 1.87–1.84 (1H, m), 1.70–1.65 (1H, m), 1.53–1.16 (7H, m), 0.77 (3H, s); ^{13}C NMR δ 169.8, 148.4, 138.2, 138.0, 126.3, 121.4, 118.5, 90.7, 57.8, 50.3, 44.1, 43.1, 38.2, 38.0, 29.5, 27.7, 27.0, 26.2, 23.0, 21.2, 11.5; MS m/z 328 (M^+, 100); HRMS calcd for $C_{21}H_{28}O_3$ 328.2039, found 328.2039.

4.3.11. Estrone (26). To a solution of **25** (10.0 mg, 3.04×10^{-2} mmol) in EtSH (1.0 mL) was added $AlBr_3$ (20.3 mg, 0.152 mmol) at room temperature, and the mixture was stirred for 30 min. The reaction was quenched by addition of water, and the mixture was extracted with AcOEt. The extract was washed with water and brine, dried, and concentrated to dryness. The residue was passed through a short pad of silica gel with hexane–AcOEt (3:1) to afford the crude alcohol (8.5 mg) as a colorless solid. To a solution of the above alcohol (8.5 mg) in acetone (1.0 mL) was added 0.5 mL of Jones reagent [CrO_3 (200 mg, 2.00 mmol) and concd H_2SO_4 (1 mL) in water (1 mL)] at room temperature. After being stirred for 30 min, the reaction mixture was diluted with water and extracted with AcOEt. The extract was washed with water and brine, dried, and concentrated to dryness. The residue was passed through a short pad of silica gel with hexane–AcOEt (3:1) to afford the crude ketone (8.3 mg) as a colorless solid. To a solution of the above ketone (8.3 mg) in MeOH (1.0 mL) was added K_2CO_3 (3.8 mg, 0.038 mmol) at room temperature. After being stirred for 1 h, the reaction mixture was diluted with water and extracted with AcOEt. The extract was washed with water and brine, dried, and concentrated to dryness. Chromatography of the residue with hexane–AcOEt (3:1) afforded **26** (7.2 mg, 89% for three steps) as colorless crystals. Mp 255–257 °C (CH_2Cl_2–hexane); IR 3595, 1734 cm^{-1}; ^1H NMR δ 7.15 (1H, d, J=8.5 Hz), 6.64 (1H, dd, J=8.5, 2.4 Hz), 6.58 (1H, d, J=2.4 Hz), 4.67 (1H, br s), 2.89–2.85 (2H, m), 2.50 (1H, dd, J=18.9, 8.5 Hz), 2.40–2.34 (1H, m), 2.28–2.21 (1H, m), 2.18–1.92 (4H, m), 1.68–1.39 (6H, m), 0.91 (3H, s); ^{13}C NMR δ 221.0, 153.5, 138.1, 132.1, 126.5, 115.3, 112.9, 50.4, 48.0, 44.0, 38.4, 35.9, 31.6, 29.5, 26.5, 25.9, 21.6, 13.9; MS m/z 270 (M^+, 94.1); HRMS calcd for $C_{18}H_{22}O_2$ 270.1620, found 270.1617.

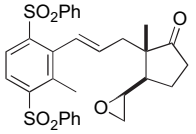
Acknowledgements

This work was supported in part by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science, and Technology, Japan, for which we are thankful.

References and notes

1. Kitagaki, S.; Ohdachi, K.; Katoh, K.; Mukai, C. *Org. Lett.* **2006**, *8*, 95–98.
2. Horner, L.; Binder, V. *Liebigs Ann. Chem.* **1972**, *757*, 33–68.
3. The tandem formation and intramolecular [4+2] cycloaddition of 1-sulfinyl-1-vinylallenes, triggered by [2,3]-sigmatropic rearrangement of the corresponding propargyl sulfenates, have been reported: (a) Okamura, W. H.; Curtin, M. L. *Synlett* **1990**, 1–9; (b) Curtin, M. L.; Okamura, W. H. *J. Org. Chem.* **1990**, *55*, 5278–5287; (c) Gibbs, R. A.; Bartels, K.; Lee, R. W. K.; Okamura, W. H. *J. Am. Chem. Soc.* **1989**, *111*, 3717–3725; (d) Gibbs, R. A.; Okamura, W. H. *J. Am. Chem. Soc.* **1988**, *110*, 4062–4063.
4. (a) Tanaka, K.; Takamoto, N.; Tezuka, Y.; Kato, M.; Toda, F. *Tetrahedron* **2001**, *57*, 3761–3767; (b) Toda, F.; Tanaka, K.; Sano, I.; Isozaki, T. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1757–1758; (c) Sugimoto, Y.; Hanamoto, T.; Inanaga, J. *Appl. Organomet. Chem.* **1995**, *9*, 369–375; (d) Inanaga, J.; Sugimoto, Y.; Hanamoto, T. *Tetrahedron Lett.* **1992**, *33*, 7035–7038; (e) Ezcurra, J. E.; Moore, H. W. *Tetrahedron Lett.* **1993**, *34*, 6177–6180; (f) Braverman, S.; Duar, Y. *J. Am. Chem. Soc.* **1990**, *112*, 5830–5837; (g) Höhn, J.; Weyerstahl, P. *Chem. Ber.* **1983**, *116*, 808–814; (h) Staab, H. A.; Draeger, B. *Chem. Ber.* **1972**, *105*, 2320–2333; (i) Bowes, C. M.; Montecalvo, D. F.; Sondheimer, F. *Tetrahedron Lett.* **1973**, 3181–3184; (j) Ben-Efraim, D. A.; Sondheimer, F. *Tetrahedron Lett.* **1963**, 313–315.
5. (a) Segura, J. L.; Martin, N. *Chem. Rev.* **1999**, *99*, 3199–3246; (b) Martin, N.; Seoane, C.; Hanack, M. *Org. Prep. Proced. Int.* **1991**, *23*, 237–272; (c) Charlton, J. L.; Alauddin, M. M.

Tetrahedron **1987**, *43*, 2873–2889; (d) Oppolzer, W. *Synthesis* **1978**, 793–802.
6. Kitagaki, S.; Katoh, K.; Ohdachi, K.; Takahashi, Y.; Shibata, D.; Mukai, C. *J. Org. Chem.* **2006**, *71*, 6908–6914.
7. The intermolecular cycloaddition reaction of the *o*-quinodimethane derived from *cis*-4-octene-2,6-diyne-1,8-diol and PhSCl was described in the review article by Grissom: Grissom, J. W.; Gunawardena, G. U.; Klingberg, D.; Huang, D. *Tetrahedron* **1996**, *52*, 6453–6518.
8. [1,5] Hydrogen-shifted product was isolated as **8′** in 29% yield after *m*-CPBA oxidation of a mixture of pericyclic reaction products: Kitagaki, S.; Ohdachi, K.; Mukai, C. Unpublished results.



8′

9. (a) Myers, A. G.; Zheng, B. *J. Am. Chem. Soc.* **1996**, *118*, 4492–4493; (b) Myers, A. G.; Zheng, B. *Org. Synth.* **1998**, *76*, 178–186.
10. Movassaghi, M.; Ahmad, O. K. *J. Org. Chem.* **2007**, *72*, 1838–1841.
11. For reviews on total syntheses of estrogens, see: (a) Zeelen, F. J. *Nat. Prod. Rep.* **1994**, *11*, 607–612; (b) Groen, M. B.; Zeelen, F. J. *Recl. Trav. Chim. Pays-Bas* **1986**, *105*, 465–487; For recent examples, see: (c) Yeung, Y.-Y.; Chein, R.-J.; Corey, E. J. *J. Am. Chem. Soc.* **2007**, *129*, 10346–10347; (d) Soorukram, D.; Knochel, P. *Org. Lett.* **2007**, *9*, 1021–1023; (e) Hu, Q.-Y.; Rege, P. D.; Corey, E. J. *J. Am. Chem. Soc.* **2004**, *126*, 5984–5986; (f) Pattenden, G.; Reddy, L. K.; Walter, A. *Tetrahedron Lett.* **2004**, *45*, 4027–4030; (g) Hanada, K.; Miyazawa, N.; Ogasawara, K. *Chem. Pharm. Bull.* **2003**, *51*, 104–106; (h) Tanaka, K.; Nakashima, H.; Taniguchi, T.; Ogasawara, K. *Org. Lett.* **2000**, *2*, 1915–1917; (i) Rigby, J. H.; Warshakoon, N. C.; Payen, A. J. *J. Am. Chem. Soc.* **1999**, *121*, 8237–8245; (j) Tietze, L. F.; Nöbel, T.; Spescha, M. *J. Am. Chem. Soc.* **1998**, *120*, 8971–8977; (k) Quinkert, G.; Del Grosso, M.; Döring, A.; Döring, W.; Schenkel, R. I.; Bauch, M.; Dambacher, G. T.; Bats, J. W.; Zimmermann, G.; Dürner, G. *Helv. Chim. Acta* **1995**, *78*, 1345–1391.
12. (a) Kametani, T.; Nemoto, H.; Ishikawa, H.; Shiroyama, K.; Matsumoto, H.; Fukumoto, K. *J. Am. Chem. Soc.* **1977**, *99*, 3461–3466; (b) Quinkert, G.; Weber, W.-D.; Schwartz, U.; Dürner, G. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 1027–1029; (c) Quinkert, G.; Schmalz, H.-G.; Walzer, E.; Gross, S.; Kowalczyk-Przewloka, T.; Schierloh, C.; Dürner, G.; Bats, J. W.; Kessler, H. *Liebigs Ann. Chem.* **1988**, 283–315.
13. The use of *t*-butyl acrylate as a Michael acceptor led to increase in stereoselectivity as well as chemical yield of the desired product compared to the reported procedure; stereoselectivity: trans/cis=6.5:1, isolated yield of trans isomer: 66%. See Ref. 12c.
14. The product was obtained as a separable mixture of diastereoisomers in a ratio of 5:1 and the desired stereoisomer was used for the next reaction. Their stereochemical assignments were unambiguously established by the NOE experiments.
15. (a) Myers, A. G.; Alauddin, M. M.; Fuhry, M. A. M.; Dragovich, P. S.; Finney, N. S.; Harrington, P. M. *Tetrahedron Lett.* **1989**, *30*, 6997–7000; (b) Hall, R. G.; Trippett, S. *Tetrahedron Lett.* **1982**, *23*, 2603–2604.
16. It would be reasonable that **22** must consist of four diastereomers. However, two products out of the four possible diastereomers were detected in a ratio of ca. 1:1 by ^{1}H and ^{13}C NMR analyses.
17. The diastereomer ratio was not determined.
18. Strazzolini, P.; Runcio, A. *Eur. J. Org. Chem.* **2003**, 526–536.
19. For Baeyer–Villiger oxidation of C-3 acetyl steroids, see: (a) Collins, M. A.; Jones, D. N. *Tetrahedron Lett.* **1995**, *36*, 4467–4470; (b) Oppolzer, W.; Roberts, D. A. *Helv. Chim. Acta* **1980**, *63*, 1703–1705; (c) Nambara, T.; Honma, S.; Akiyama, S. *Chem. Pharm. Bull.* **1970**, *18*, 474–480.
20. For $Sc(OTf)_3$-catalyzed Baeyer–Villiger oxidation, see: Kotsuki, H.; Arimura, K.; Araki, T.; Shinohara, T. *Synlett* **1999**, 462–464.
21. (a) Posner, G. H.; Hulce, M.; Mallamo, J. P.; Drexler, S. A.; Clardy, J. *J. Org. Chem.* **1981**, *46*, 5244–5246; (b) Quinkert, G.; Schwartz, U.; Stark, H.; Weber, W.-D.; Baier, H.; Adam, F.; Dürner, G. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 1029–1030; (c) Kametani, T.; Matsumoto, H.; Nemoto, H.; Fukumoto, K. *J. Am. Chem. Soc.* **1978**, *100*, 6218–6220; (d) Taber, D. F.; Raman, K.; Gaul, M. D. *J. Org. Chem.* **1987**, *52*, 28–34; (e) Groth, U.; Halfbrodt, W.; Kalogerakis, A.; Köhler, T.; Kreye, P. *Synlett* **2004**, 291–294; (f) Urban, E.; Knühl, G.; Helmchen, G. *Tetrahedron* **1996**, *52*, 971–986.