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Efficient Construction of Highly Substituted and Stereodefined *cis*-Fused Lactones

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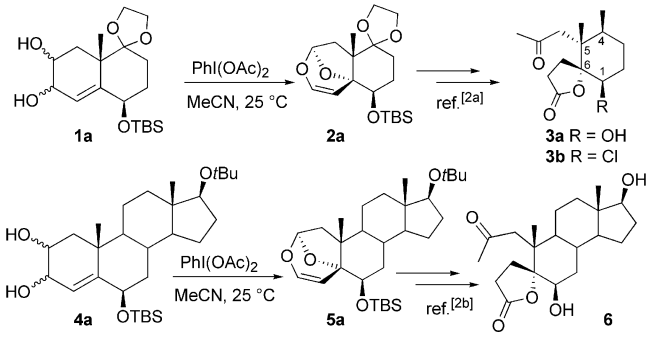
Dedicated to Professor Henri Kagan on the occasion of his 80th birthday

Keywords: Epoxidation / Domino reactions / Lactones / Terpenoids / Fused-ring systems

The methodology described in this paper involves the epoxidation of cyclic ene-acetals to spontaneously generate 6α-hydroxy-bis-acetals that could serve as precursors for a Cannizzaro-type rearrangement, yielding bis-angularly substituted *cis*-fused lactones. Both the oxidizing reagent, *m*-CPBA or $NaBO_3$, and the substitution pattern can be important in determining the course of the epoxidation/ring-opening sequence, with $NaBO_3$ being the ideal electrophilic oxidant for the epoxidation/spontaneous ring-opening/ring-system interchange sequence.

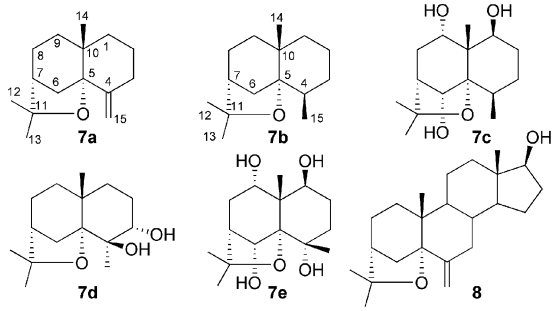
Introduction

Through our efforts towards the total synthesis of norsesquiterpene spirolactones **3a** and **3b**, we investigated the $PhI(OAc)_2$-mediated oxidative cleavage of unsaturated diol **1a** (obtained from (*S*)-(+)-Wieland–Miescher ketone), which provided required tricyclic framework **2a** (Scheme 1). We then extended the synthetic usefulness of this domino[1] approach to the synthesis of norsesquiterpene spirolactone–testosterone hybrids of type **6** starting from steroidal unsaturated diol **4a** as the domino precursor. This provided a convenient route for the synthesis of 1-*epi*-pathylactone A (**3a**, R = OH),[2a] thus invalidating the assigned C1 configuration for pathylactone A,[2c,2d] the carbon skeleton of nardosinane (**3b**),[2e] and the norsesquiterpene spirolactone–testosterone hybrid **6**.[2b]



Scheme 1.

Thus, a methodology has been developed within our group that has proven valuable for the construction of elaborated six-membered rings contained in natural as well as unnatural products. A similar methodology could also be employed for the preparation of advanced building blocks for the agarofuran sesquiterpene skeleton (i.e., **7**)[3–5] as well as for hybrid molecules of type **8**[6] starting from the same tricyclic frameworks **2a** and **5a**, respectively (Scheme 2).



Scheme 2.

The constant structural motif in the β-agarofuran series is a *trans*-fused decalin, which incorporates two adjacent quaternary centers at C5 and C10. The same ring system, albeit with different locations of unsaturation and oxygen functionality, is found in a large number of related molecules. Inspired by the previous contributions reported by Danishefsky,[7] Vankar,[8] and Goti[9] on the epoxidation of

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glycals, we sought to exploit our domino approach along with a facile preparation of bicyclic lactones that was developed in our laboratory[10] for the synthesis of various agarofuran precursors and hybrid molecules.

Close precursors of β-agarofuran (**7a**), dihydro-β-agarofuran (**7b**), and its congeners celorbicol (**7c**), boariol (**7d**), and 4β-hydroxycelorbicol (**7e**), as well as various derivatives of β-agarofuran–testosterone hybrid **8** (Scheme 1) could be accessed by applying the proposed epoxidation/spontaneous ring-opening/ring-system interchange sequence portrayed in Figure 1 to bicyclic and steroidal unsaturated diols of types **1** and **4**.

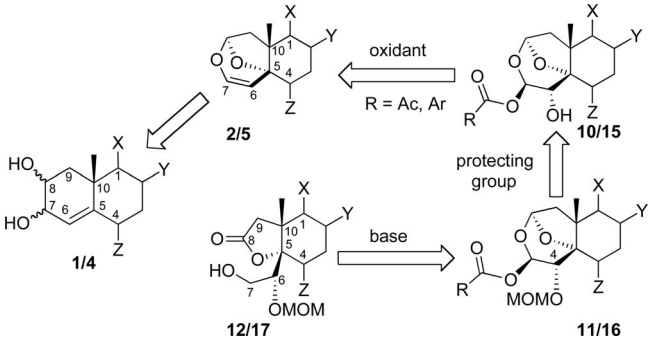


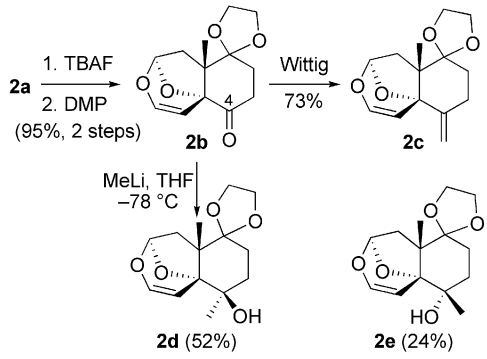
Figure 1. Short and efficient reaction sequence from unsaturated bicyclic diols (**1**/**4**) to *cis*-fused bicyclic lactones (**11**/**16**).

We report here an approach toward conveniently functionalized *cis*-fused lactone building blocks of type **12**/**17** starting from type **2**/**5** domino products by a simple three-step procedure in which sodium perborate[11] serves as an ideal olefin oxidant and potassium carbonate as a Cannizzaro-type oxidoreduction promoter (Figure 1).

Results and Discussion

With the aim to investigate their reactivity pattern, a series of tricyclic and pentacyclic ene-acetals of type **2** and **5** (half-cascade or interrupted domino products used in our earlier studies) were prepared in quantity from the corresponding domino precursors **1** and **4**, respectively. Key compounds **2a** and **5a**, obtained in one synthetic operation upon treatment of **1a** and **4a** with $PhI(OAc)_2$ (1.2 equiv.) in acetonitrile, can be easily isolated, stored without any special care, and further elaborated, thus allowing different functional group interconversion in a stereodefined fashion. We hypothesized that cyclic ene-acetals **2a** and **5a** might behave as stereochemically biased building blocks provided that their reactivity could be suitably controlled. To examine this possibility, we investigated their epoxidation and their trend to undergo a Cannizzaro-type oxidoreduction upon orthogonal protection and subsequent mild base treatment. To that end, we chose *m*-CPBA and $NaBO_3$ as electrophilic oxidants and carried out initial experiments with *m*-CPBA.

Access to requisite substrates **2b**–**h** with varying substitution and steric requirements was readily achieved from **2a** through trivial transformations (Schemes 3 and 5; see also the Supporting Information). Fluoride-mediated deprotection and subsequent Dess–Martin oxidation of **2a** provided requisite C4 ketone **2b** used for the synthesis of **2c**–**e**. Treatment of **2b** with methyllithium at low temperature afforded the corresponding epimeric methyl carbinols **2d** and **2e** in 76% yield and a 2:1 diastereoselectivity. Diastereomerically pure **2e** (m.p. 132–134 °C, heptane/Et_2O) could be obtained after purification of the crude reaction mixture by column chromatography, and its C4 configuration was proved by ^1H NMR spectroscopy by using spatial proximity effect measurements. The structure of crystalline carbinol **2d** (m.p. 123–125 °C, heptane/Et_2O), not surprisingly the major epimer, was confirmed by a single-crystal X-ray diffraction study, which showed that this compound arises from α-face attack of the nucleophile at C4 (Figure 2).



Scheme 3.

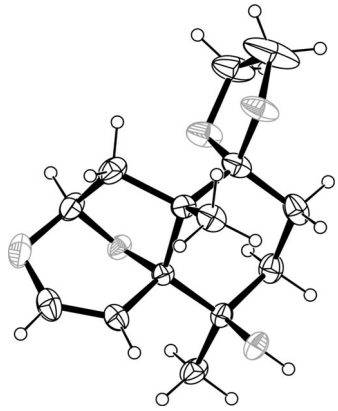
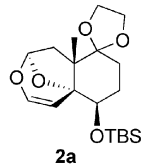
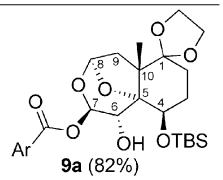
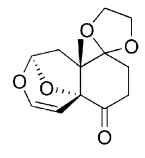
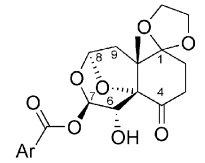
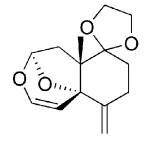
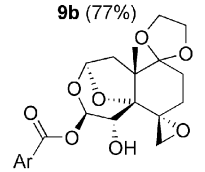
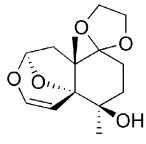
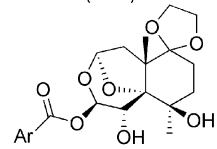
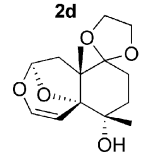
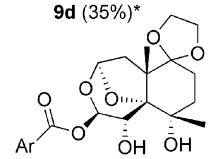
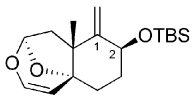
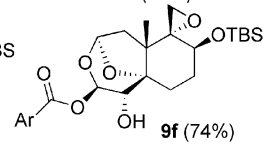


Figure 2. ORTEP drawing of **2d** (major carbinol, oxygen functionalities in light gray).

Substrate **2c** was obtained uneventfully from **2b** by Wittig olefination. Substrate **2f** (Table 1) bearing an olefin and a protected alcohol was prepared from the known C1 olefin[10b] through allylic oxidation at C2 and subsequent TBS protection (see the Supporting Information). Cyclic ene-acetals **2a**–**h** appear to possess the favorable attributes anticipated for highly regio- and stereoselective serial epoxidation/ring opening and could thus be used as stereogenic scaffolds. Initial studies focused upon *m*-CPBA-treatment of half-cascade intermediates **2a**–**f** as model compounds (Table 1). This involved epoxidation at the sterically less screened face of the C6–C7 enol ether as well as the exocy-

clic olefins at C1 and C4, and subsequent diaxial nucleophilic opening of the transient epoxide to form the corresponding 6α-hydroxy-7β-aroyloxy bis-acetals **9a**–**f**. Upon treatment of **2a** with *m*-CPBA (1.2 equiv.) in CH_2Cl_2 at room temperature, corresponding bis-acetal **9a** (m.p. 110–112 °C, heptane/Et_2O), whose structure was secured by X-ray analysis (Figure 3), was isolated in 82% yield (96% based on recovered starting material). The sense of selectivity favoring **9a** is consistent with α-face attack (the more exposed face of the π bond at C6–C7) for the peracid addition process setting the requisite stereochemistry at C6 (agarofuran numbering).[12]

Table 1. Reactions conducted with *m*-CPBA (2.0 mmol) and substrate **2b**–**f** (1.0 mmol) in CH_2Cl_2 (5 mL) at 25 °C.[a]

Entry	Substrate	Product (% yield)
1	 **2a**	 **9a** (82%)
2	 **2b**	 **9b** (77%)
3	 **2c**	 **9c** (66%)
4	 **2d**	 **9d** (35%)*
5	 **2e**	 **9e** (95%)
6	 **2f**	 **9f** (74%)

[a] ***9d** was characterized as its corresponding C6 acetate. Ar stands for *m*-ClC_6H_4.

Oxidation of substrates **2b**–**f** with *m*-CPBA in CH_2Cl_2 gave hydroxyesters **9** as single products in each case through in situ nucleophilic epoxide opening, whereas no trace of any intermediate epoxides was noted. NMR spectroscopic analysis did permit the assignment of both regio- and stereochemistry.

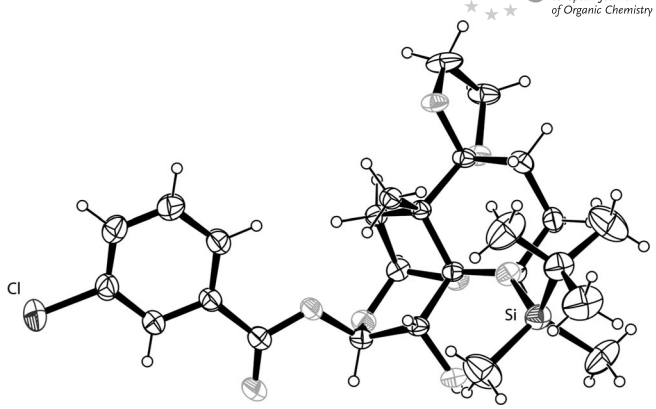


Figure 3. ORTEP drawing of **9a** (oxygen functionalities in light gray).

The results in Table 1 show that *m*-CPBA is highly efficient in controlling both the regio- and stereoselectivity of oxyfunctionalization. No side products were observed; instead, 7β-aroyloxy compounds were isolated (35–95% yield) along with various amounts (10–20%) of unreacted starting material. Templates bearing both an enol and an alkene group such as **2c** and **2f** reacted cleanly with *m*-CPBA, allowing stereoclean construction of highly functionalized bicyclic bis-acetals **9c** and **9f** bearing four and six contiguous stereogenic centers, respectively. In the one-step transformations from **2d** to **9d** and from **2e** to **9e**, both C4 configurations required for boariol (**7d**) and 4β-hydroxycelorbicol (**7e**) were secured.

At the outset, we were concerned with the scope of the sequential epoxidation/ring-opening process, whereas the pending difficulty for the following Cannizzaro-type oxidoreduction was not anticipated. Even though *m*-CPBA provided complete regioselectivity, difficulties were encountered during subsequent transformation; basic hydrolysis (K_2CO_3, MeOH/H_2O, 25 °C) did not give the desired lactones even under forcing conditions (*idem* for the 6-MOM protected bis-acetals). This disappointing result encouraged us to explore more selective options for the planned three-reaction process (serial epoxidation/nucleophilic ring opening/mild basic treatment, Figure 1). Our second choice as electrophilic oxidant, $NaBO_3$ (SPB),[13] did the job perfectly, except as far as the regioselectivity was concerned. Indeed, a C4 substitution (of any nature) was necessary to ensure regioselectivity in the epoxide-opening step of the process.[14] After examination of several options, the most reliable and effective procedure was found to be the room-temperature treatment in AcOH with the reagent (2 equiv.). The optimized procedure involved addition of $NaBO_3$ to a solution of **2a** in AcOH and stirring at room temperature (TLC monitoring). This afforded desired acetoxy-bis-acetal **10a** in satisfactory yields (68% along with 17% of recovered starting material) and with an isomer profile identical to that derived from *m*-CPBA. After purification by flash chromatography the structure of the crystalline 7β-acetoxy-6α-hydroxy bis-acetal **10a** (m.p. 97–98 °C, heptane/ether) was first deduced by 2D NMR experiments, particularly NOESY spectra, and was later confirmed by single-crystal X-ray diffraction (Figure 4).

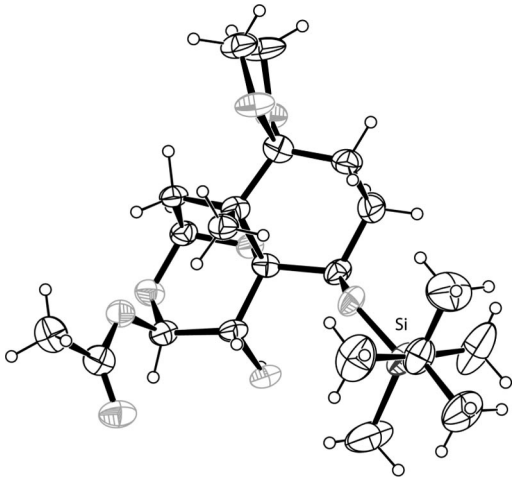
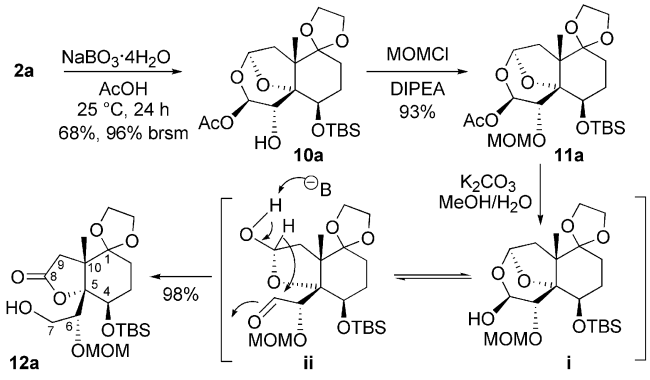


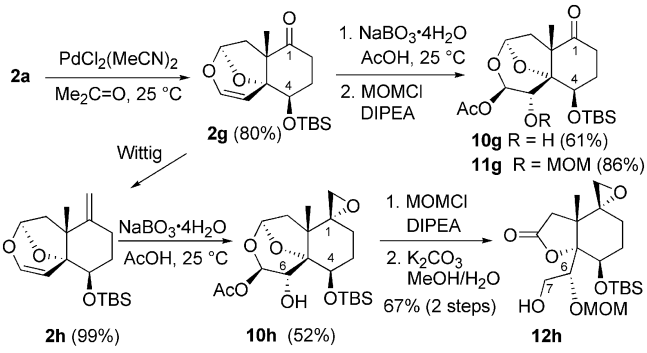
Figure 4. ORTEP drawing of **10a** (oxygen functionalities in light gray).

The essence of our strategy toward the agarofuran backbone is depicted in Scheme 4.[15] Hence, conversion of **10a** into the corresponding MOM-protected **11a** and subsequent mild base treatment (K_2CO_3, MeOH/H_2O, 2 h, 25 °C) afforded targeted bicyclic lactone **12a** in 98% yield. A reasonable scheme to unveil the second quaternary center at C5 and to set the correct C6 configuration of the agarofuran skeleton from **2a** would involve intramolecular Cannizzaro-type oxidoreduction[16] of intermediate lactol **i** through transient hemiacetal **ii**.



Scheme 4. Ring-system interchange through mild base initiated intramolecular hydride transfer.

To highlight the method, the above synthetic strategy was applied to substrates **2g** and **2h** bearing a free carbonyl group and an exocyclic olefin, respectively, both prepared from known **2a** by using standard literature procedures (Scheme 5 and Supporting Information). The importance of steric accessibility of the transient epoxide was confirmed by the regioselectivity observed for substrates **2g** and **2h**, which furnish solely acetoxy acetals **10g** and **10h**. Thus, under the standard epoxidation/ring-opening conditions ($NaBO_3·4H_2O$, AcOH, 25 °C) the C4 substitution of the substrates dictated the regiochemical outcome through steric effects, whereas no trace of lactone formation by Baeyer–Villiger oxidation of **2g** was detected.[13] MOM protection at C6 and subsequent basic treatment of **10h** (K_2CO_3, MeOH/H_2O, 25 °C) ultimately allowed construction of the highly functionalized bicyclic lactone **12h**.



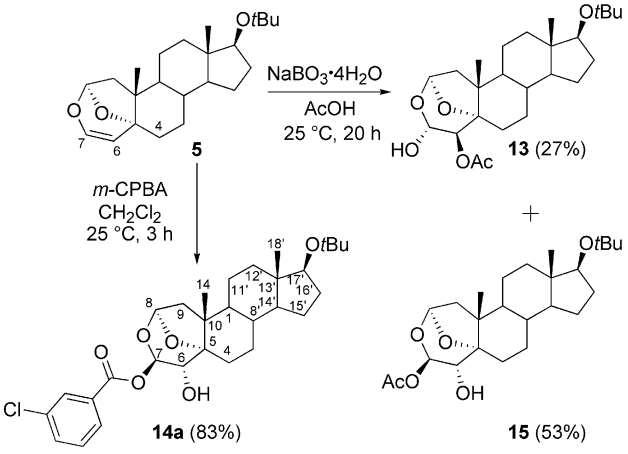
Scheme 5.

A key discovery in this first part was that conveniently functionalized cyclic ene-acetals **2** undergo easy regio- and stereoselective epoxidation/spontaneous ring-opening upon treatment with $NaBO_3$ in acetic acid, leading directly to 6α-hydroxy-7β-acetoxy acetals **10** in good to high yields. Still, the most interesting facet of this reaction is the ease of subsequent mild base promoted ring-system interchange, leading to highly functionalized *cis*-fused lactone frameworks. This approach provides easy access to the desired agarofuran building blocks, as starting unsaturated diols **1** (Scheme 1) are readily available from (*S*)-(+)-Wieland–Miescher ketone.[2a]

Extension of the Method toward the Synthesis of Agarofuran–Testosterone Hybrids

Given the success in forming *cis*-fused bicyclic lactones from half-cascade intermediates **2**, it seemed to us that this approach could well prove to be adaptable to the synthesis of hybrid molecules. Accordingly, a second set of experiments was conducted in which the required half-cascade intermediates **5**[10b] prepared from testosterone were subjected to the epoxidation/ring-opening sequence.

Analogous results were obtained for the epoxidation of steroidal substrate **5**, as both *m*-CPBA and $NaBO_3$ were successfully employed in the epoxidation/in situ opening studies in CH_2Cl_2 and AcOH, respectively. The behavior of $NaBO_3$, which displayed no substantial selectivity thus leading to a mixture of regioisomeric products **13** and **15** under identical conditions, is again in sharp contrast with that of *m*-CPBA. The stereostructures of the resulting products (easily separable by chromatography) were inferred from their ^1H NMR spectra, as the C6 and C7 proton resonances of regioisomers **13** and **15** are considerably different (Scheme 6).



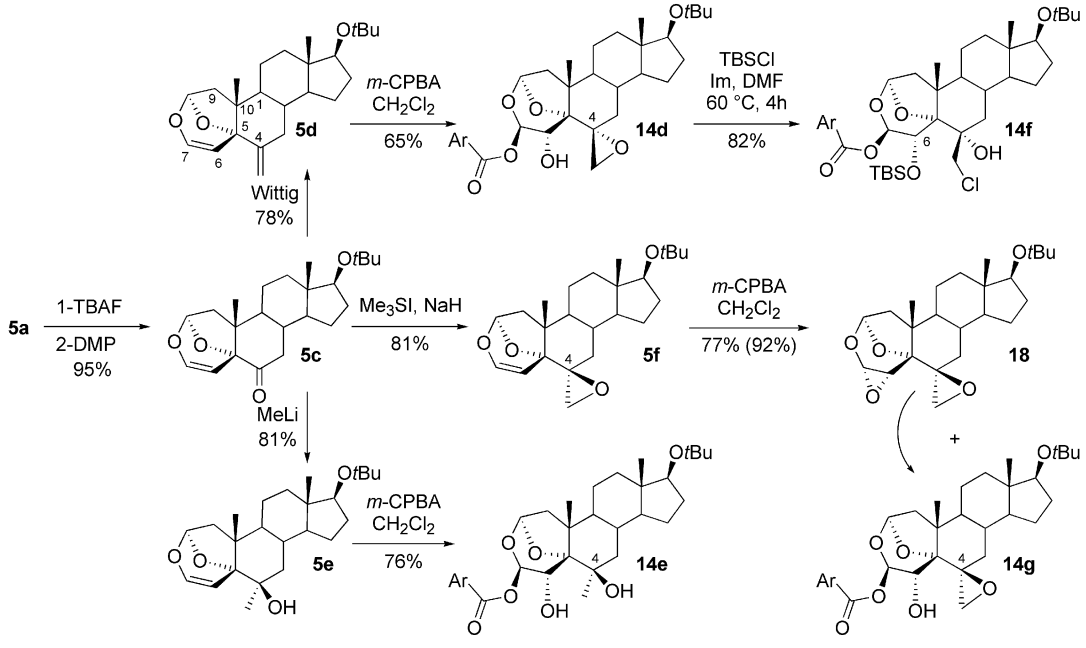
Scheme 6.

The sense of stereoselectivity favoring **14** and **15** is consistent with α-face attack of the peracid followed by *trans*-diaxial epoxide opening. Obviously, nucleophilic attack of *m*-CPBA at the C6 position of the transient epoxide is sterically more obstructed than attack by acetic acid.

The substrates used in this part of the study were synthesized in an efficient manner from known domino product **5a**[2b] by the route illustrated in Scheme 7. Fluoride-promoted desilylation and subsequent Dess–Martin oxidation afforded cleanly desired ketone **5c**, which served as a key intermediate for the construction of the required templates. Corey–Chaykovsky epoxidation[17] of **5c** thus obtained afforded **5f**; Wittig olefination furnished **5d**, whereas methyllithium addition cleanly afforded methyl carbinol **5e** as a single isomer. Finally, **5b** (Scheme 8) was obtained by transprotection achieved in two steps from **5a** (BF_3·Et_2O in PhMe followed by MOMCl). Nucleophilic epoxidation under Corey–Chaykovsky conditions (indirectly) or methyllithium addition of **5c** ensured access to C4 α-methyl carbinol (**5f** and **14e**), whereas electrophilic epoxidation of **5d** provided access to the epimeric C4 oxygenated quaternary center via epoxide **14d**. Unsurprisingly, alkylation (**5c** to **5e**) and epoxidations (**5c** to **5f**, and **5d** to **14d**) did show excellent levels of stereoselectivity. This allowed modular construction of the C4 oxygenated quaternary center, thus providing access to precursor molecules for either type **7d** or **7e** agarofuran–testosterone hybrids (Scheme 2).

As with cyclic acetals **2**, the intermediate epoxides were not isolable under the reaction conditions (using either *m*-CPBA or $NaBO_3$) except in the case of substrate **5f**, which showed a slightly different reactivity pattern. Indeed, the *m*-CPBA-mediated epoxidation of **5f** is unusual in that for this substrate the transient epoxide does not immediately undergo ring opening. In this specific case, the reaction was incomplete, as the intermediate epoxide was resistant to esterification, thus allowing bis-epoxy cyclic acetal **18** to be isolated and characterized. However, we observed that the latter, originally obtained as a minor product, was gradually converted into **14g** upon prolonged reaction time.

Interestingly, subjection of substrates **5d** and **5e** to *m*-CPBA-mediated epoxidation proceeded uneventfully, leading exclusively to **14d** and **14e** in good isolated yields. Structural assignment of **14d** was determined by X-ray analysis of chlorhydrine **14f** (Figure 5b), which was accidentally obtained upon attempted TBS protection of the hydroxy group at C6 (Scheme 7).[18] MeLi addition to **5c** provided **5**e with complete facial selectivity; the incoming nucleophile was directed to approach from the α-face (rationalized with chelation and the unfavored β-face Bürgi–Dunitz trajectory,



Scheme 7. Towards the main representatives of agarofuran sesquiterpene–testosterone hybrids: varying the C4 configuration.

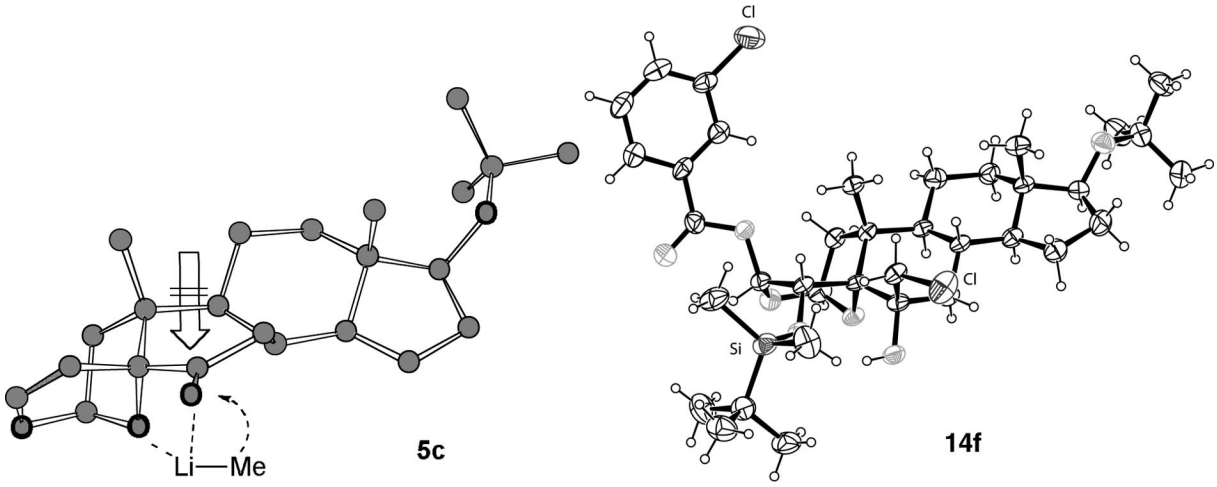
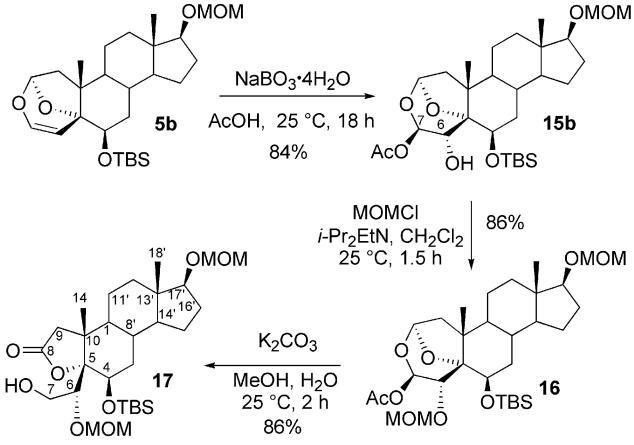


Figure 5. (a) Rationalization of facial selectivity upon nucleophilic attack on **5c** (PM3 minimized structure). (b) ORTEP drawing of **14f** (oxygen functionalities in light gray).

Figure 5a). *m*-CPBA-mediated epoxidation then led to **14e**, whose structure was confirmed by NMR spectroscopy and by analogy with the compounds obtained from **2e** and **2d** (Scheme 3).

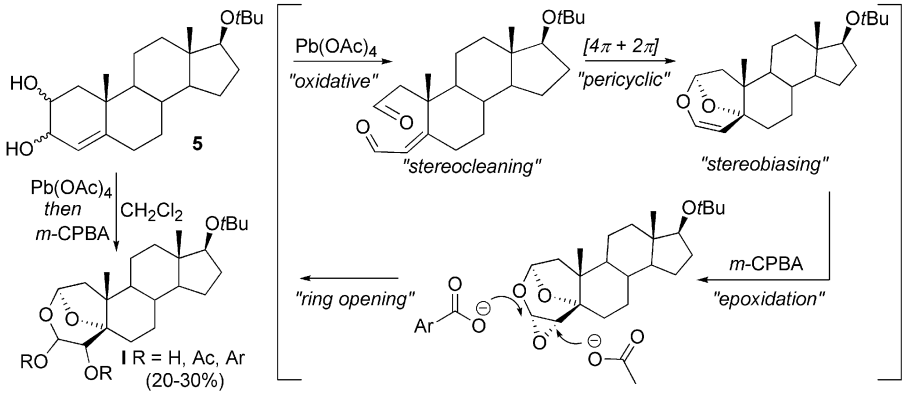
As discussed above, due to practical problems, $NaBO_3$ was employed as a potential replacement for *m*-CPBA. In the reaction pathway depicted in Scheme 8, the C6,C7 (agarofuran numbering) oxygenated compound **15b** is formed with complete selectivity (both regio- and stereo-), as the starting ene-acetal is functionalized at C4. This significant orientation effect of the allylic OTBS substituent at C4 is not surprising considering the distance of this bulky group from the transient epoxide reaction center. Moreover, its influence on the conformation of the cyclohexane is an important determinant of acetoxy accessibility.[19]



Scheme 8. Synthesis of key intermediate **17** for agarofuran–testosterone hybrids.

Finally, having probed the susceptibility of a range of cyclic ene-acetals toward the sodium perborate mediated epoxidation, extension to a one-pot, three-component domino protocol was investigated. Hence, oxidative cleavage of diol **5** with $Pb(OAc)_4$ in CH_2Cl_2 (the solvent is compatible with both reagents) triggered a hetero-[4π + 2π] cycloaddition in which *m*-CPBA epoxidized the enol ether to afford directly bis-acetal backbone **I**, though in very low yields and as mixtures of aroylated and acetylated derivatives (the acetyl group comes from the domino promoter). The latter, added in a consecutive way (one-pot reaction) offered no improvement and appeared to diminish the yield and purity of the isolated product mixture (Scheme 9).

In summary, we have shown that variously functionalized bicyclic or tetracyclic ene-acetals were amenable to this epoxidation/spontaneous ring-opening reaction in which



Scheme 9. Attempted "one-pot" oxidative cleavage/epoxidation/ring opening.

hydroxy and acyloxy (aroyloxy) substituents are regio- and stereoselectively installed at C6 and C7, respectively, thus yielding a variety of orthogonally protected α-hydroxy-bis-acetals. The angular substituent at C10, in combination with C4 substitution, enables a high measure of steric manipulation in directing the attacking oxidant and the sense of spontaneous epoxide ring opening.

Conclusions

Overall, a methodology has been developed that enables the construction of useful stereodefined ring systems. The ready availability of starting *vicinal* diols **1a** and **4a**, together with the effectiveness of the interrupted domino transformations offering cleanly **2a** and **5a**, was vital to the development of the route presented in this work. Considering their special structural features, the investigated substrates offer promising openings to explore their propensity in regio- and stereoselective epoxidations (reagent and substrate selectivity, respectively). The C10 methyl group along with the system's cavity dictates π-facial selectivity, whereas C4 substitution, other than hydrogen, promotes regioselective ring opening when $NaBO_3$ is used as the electrophilic oxidant. In the course of the present study, we discovered that the initially used *m*-CPBA is not compatible with the mild base induced Cannizzaro oxidoreduction part of the serial epoxidation/ring opening/intramolecular hydride transfer and that only $NaBO_3$ (SPB) is capable of achieving the whole sequence. Reactivity can be increased by inclusion of olefinic functional groups, and the process is compatible even with a free carbonyl group.

Experimental Section

General: "Usual workup" means washing of the organic layer with brine, drying with anhydrous $MgSO_4$, and concentrating in vacuo under reduced pressure. Melting points were determined with a Büchi B- 540 apparatus. IR spectra were recorded with a Perkin–Elmer Spectrum BX instrument with an FTIR system. Optical Rotations were measured with a JASCO- 810 polarimeter by using a cell with a 1-dm-length path. NMR spectra were run in $CDCl_3$ unless otherwise noted. Experimental evidence favoring the structures investigated came from a comprehensive range of ^1H and ^{13}C NMR data (500/125 and 300/75 MHz respectively, 1D and 2D experiments) and corroborated by spatial proximity (n.O.e). For all compounds investigated, multiplicities of ^{13}C resonances were assigned by the DEPT technique. ^1H chemical shifts are expressed in ppm downfield from TMS using the residual nondeuterated solvent as internal standard ($CDCl_3$, ^1H: 7.26 ppm). ^{13}C chemical shifts are reported relative to $CDCl_3$ triplet centered at 77.0 ppm.

Preparation of Bicyclic Lactone 12a by the Three-Reaction Sequence: $NaBO_3·4H_2O$-mediated epoxidation of substrate **2a** (170 mg, 0.46 mmol) was carried out in AcOH (10 mL) at room temperature by using the general procedure (24 h, see the Supporting Information) to give, after SiO_2 flash column chromatography (heptane/EtOAc, 1:1), 6α-hydroxy-7β-acetoxy bis-acetal **10a** (138 mg, 68%) along with recovered starting material (28 mg, 17%). Data for **10a**: White solid; m.p. 97–98 °C (heptane/Et_2O). $[\alpha]_D^{20}$ = +9.3 (*c* = 1.0, $CHCl_3$). IR (film): ṽ = 3447, 2954, 2935, 2889, 2858, 1746, 1471, 1445, 1362, 1248, 1226, 1079, 1015, 1003, 913, 836, 778, 729, 672 cm^{-1}. ^1H NMR (500 MHz): δ = 0.10 (s, 3 H, Me-Si), 0.12 (s, 3 H, Me-Si), 0.90 (s, 9 H, *t*Bu), 1.42 (m, 1 H, H2), 1.50 (s, 3 H, Me14), 1.67 (ddd, *J* = 2.7, 3.0, 13.9 Hz, 1 H, H3), 1.90 (dt, *J* = 2.5, 13.8 Hz, 1 H, H3), 2.03 (dd, *J* = 2.9, 12.1 Hz, 1 H, H2), 2.10 (s, 3 H, *Me*C=O), 2.14 (m, 1 H, H9), 2.35 (dd, *J* = 6.2, 14.3 Hz, 1 H, H9), 2.46 (m, 1 H, OH), 3.69 [m, 4 H, O(CH_2)$_2$O], 4.00 (dt, *J* = 1.3, 4.8 Hz, 1 H, H4), 4.31 (t, *J* = 2.2 Hz, 1 H, H6), 5.36 (d, *J* = 6.2 Hz, 1 H, H8), 6.03 (s, 1 H, H7) ppm. ^{13}C NMR (125 MHz): δ = –5.2 (Me-Si), –4.8 (Me-Si), 17.6 (Me), 18.1 (C_q-*t*Bu), 21.4 (C14), 23.1 (C2), 25.8 (3 C, *t*Bu), 26.4 (C3), 39.1 (C9), 49.0 (C10), 50.7 (C1), 63.1 and 65.2 [O(*C*H_2)$_2$O], 66.5 (C6), 66.7 (C4), 88.1 (C5), 95.6 (C7), 100.1 (C8), 111.8 (C1), 169.1 ppm. MS (ESI+, MeOH): *m*/*z* (%) = 467.2 (100) $[M + Na]^+$. HRMS (ESI+, MeOH): calcd. $C_{21}H_{36}O_8NaSi$ 467.2077; found 467.2065. $C_{21}H_{36}O_8Si$ (444.22): calcd. C 56.73, H 8.16; found C 54.45, H 7.76. MOM protection at C6 was carried out on **10a** (2.5 g, 5.65 mmol) thus obtained in CH_2Cl_2 (20 mL) by adding chloromethyl methyl ether (2.5 mL, 33.9 mmol) and diisopropylethylamine (6.3 mL, 36.1 mmol), and stirring for 1 h at 25 °C. Usual workup and purification by flash chromatography (SiO_2; heptane/EtOAc, 7:3) afforded the corresponding MOM-protected alcohol **11a** (2.50 g, 93%). Yellow oil. $[\alpha]_D^{20}$ = +30.0 (*c* = 1.0, $CHCl_3$), IR (film): ṽ = 2953, 1748, 1445, 1227, 1150, 1103, 1034, 1050, 914, 828, 774 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 0.07 (s, 3 H, Me-Si), 0.12 (s, 3 H, Me-Si), 0.90 (s, 9 H, *t*Bu), 1.46 (m, 1 H, H2), 1.49 (s, 3 H, Me14), 1.71 (m, 1 H, H3), 1.97 (m, 2 H, H3, H2), 2.11 (s, 3 H, *Me*C=O), 2.13 (s, 1 H, H9), 2.43 (dd, *J* = 6.3, 14.3 Hz, 1 H, H9), 3.46 (s, 3 H, CH_3-OCH$_2$O), 3.84 (s, 1 H, H6), 3.94 [m, 4 H, O(CH_2)$_2$O], 4.48 (s, 1 H, H4), 4.89 and 4.92 (ABq, *J* = 6.7 Hz, 2 H, OCH_2OCH$_3$), 5.38 (d, *J* = 6.1 Hz, 1 H, H8), 6.35 (s, 1 H, H7) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = –5.2 (Me-Si), –3.1 (Me-Si), 17.8 (Me14), 18.3 (C_q-*t*Bu), 21.3 (CH_3-OAc), 23.4 (C2), 25.5 (C3), 26.6 (3 C, *t*Bu), 39.1 (C9), 49.5 (C_q10), 56.0 (*C*H_3-OCH$_2$O), 63.1 and 65.1 [O(*C*H_2)$_2$O], 67.1 (C4), 74.8 (C6), 87.5 (C_q5), 93.6 (C7), 98.6 (O*C*H_2-OCH$_3$), 99.5 (C8), 111.7 (C_q9), 168.9 ppm. MS (ESI+, MeOH): *m*/*z* (%) = 511.2 (100) $[M + Na]^+$. HRMS (ESI+, MeOH): calcd. for $C_{23}H_{40}O_9NaSi$ 511.2339; found 511.2329. To a stirred solution of **11a** (1.10 g, 2.25 mmol) in a mixture of methanol (140 mL) and water (14 mL) was added potassium carbonate (3.10 g, 22.5 mmol). The resulting mixture was stirred at room temperature for 1 h. After removing solvents without heating, dilution with EtOAc, usual workup, and chromatography on silica gel (heptane/EtOAc, 4:1) bicyclic lactone **12a** (0.98 g, 98%) was obtained as a colorless oil. $[\alpha]_D^{20}$ = +34.3 (*c* = 1.0, $CHCl_3$), IR (film): ṽ = 3469, 2952, 1775, 1462, 1231, 1104, 1042, 988, 834, 776, 730, 670 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 0.07 (s, 3 H, Me-Si), 0.15 (s, 3 H, Me-Si), 0.91 (s, 9 H, *t*Bu), 1.35 (s, 3 H, Me14), 1.62 (m, 2 H, 2 H2), 1.84 (m, 3 H, H8, 2 H3), 2.45 (m, 2 H, 2 H9), 3.44 (s, 3 H, CH_3-OCH$_2$O), 3.90 [m, 3 H, H6, O(CH_2)$_2$O], 4.02 [m, 5 H, 2H7, H4, O(CH_2)$_2$O], 4.59 and 4.74 (ABq, *J* = 6.7 Hz, 2 H, OCH_2OCH$_3$) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = –5.1 (Me-Si), –4.9 (Me-Si), 17.8 (C_q-*t*Bu), 19.2 (C14), 25.6 (3 C, *t*Bu), 26.2 (C8), 27.9 (C7), 39.9 (C1), 49.9 (C_q10), 55.8 (*C*H_3-OCH$_2$O), 62.4 (C7), 64.5 and 64.6 [O(*C*H_2)$_2$O], 73.3 (C4), 89.2 (C6), 92.7 (C_q5), 99.1 (O*C*H_2-OCH$_3$), 110.9 (C_q5), 175.7 ppm. MS (ESI+, MeOH): *m*/*z* (%) = 469.2 (100) $[M + Na]^+$. HRMS (ESI+, MeOH): calcd. for $C_{21}H_{38}O_8NaSi$ 469.2234; found 469.2219.

Preparation of Steroidal Lactone 17 by the Three-Reaction Sequence: $NaBO_3·4H_2O$-mediated epoxidation of substrate **5b** (90 mg, 0.25 mmol) was carried out proceeding as above (18 h) to give, after SiO_2 flash column chromatography (heptane/EtOAc, 1:1), **15b** (92.3 mg, 84%). Colorless oil. $[\alpha]_D^{20}$ = 39.1 (*c* = 1.1, $CHCl_3$). IR

(film): ṽ = 3431, 2950, 2926, 2853, 1747, 1470, 1460, 1388, 1361, 1330, 1247, 1221, 1164, 1152, 1098, 1071, 1046, 1018, 928, 834, 781, 732, 648 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.00 (s, 3 H, Me-Si), 0.02 (s, 3 H, Me-Si), 0.74 (s, 3 H, Me18′), 0.82 (s, 9 H, *t*Bu), 0.89 (m, 1 H, H14′), 1.02 (m, 1 H, H12′), 1.13 (dt, *J* = 1.9, 5.7 Hz, 1 H, H1), 1.18 (s, 3 H, Me14), 1.20 (m, 2 H, H15′, H11′), 1.30 (m, 2 H, H16′, H3), 1.44 (td, *J* = 3.5, 12.3 Hz, 1 H, H15′), 1.52 (m, 1 H, H3), 1.59 (td, *J* = 3.2, 13.9 Hz, 1 H, H2), 1.67 (dd, *J* = 2.3, 11.3 Hz, 1 H, H12′), 1.82 (td, *J* = 3.2, 12.3 Hz, 1 H, H16′), 1.98 (dd, *J* = 6.2, 14.1 Hz, 1 H, H9), 2.03 (s, 3 H, Me), 2.22 (d, *J* = 14.1 Hz, 1 H, H9), 2.70 (d, *J* = 11.1 Hz, 1 H, OH), 3.27 (s, 3 H, C*H*$_3$OCH$_2$O), 3.45, (t, *J* = 8.2 Hz, 1 H, H17′), 3.80 (d, *J* = 11.1 Hz, 1 H, H6), 4.31 (t, *J* = 2.9 Hz, 1 H, H4), 4.58 (ABq, *J* = 8.0 Hz, 2 H, OC*H*$_2$-OCH$_3$), 5.28 (d, *J* = 5.4 Hz, 1 H, H8), 5.95 (s, 1 H, H7) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = –5.2 (Me-Si), –4.6 (Me-Si), 11.6 (C18′), 15.1 (C14), 17.9 (C$_q$-*t*Bu), 21.3 (C11′), 21.4 (C14), 23.1 (C15′), 25.8 (3 C, *t*Bu), 28.1 (C2), 29.0 (C16′), 33.9 (C3), 37.4 (C12′), 42.8 (C10), 43.6 (C13′), 45.2 (C8′), 50.2 (C1), 51.8 (C14′), 55.0 (*C*H$_3$O-CH$_2$O), 66.6 (C6), 66.8 (C4), 86.4 (C5), 86.5 (C17′), 95.5 (C7), 95.9 (O*C*H$_2$-OCH$_3$), 99.3 (C8), 169.0 ppm. MS (ESI+, MeOH): *m*/*z* (%) = 577.3 (100) [M + Na]$^+$. HRMS (ESI+, MeOH): calcd. for $C_{29}H_{50}O_8NaSi$ 577.3173; found 577.3176. $C_{29}H_{50}O_8Si$ (554.32): calcd. C 62.78, H 9.08; found C 61.08, H 7.43. MOM protection at C6 was carried out on **15b** (210 mg, 0.37 mmol) as described above. Purification by flash chromatography (SiO_2; heptane/EtOAc, 9:1) afforded the corresponding MOM-protected alcohol **16** (189.3 mg, 86%). Colorless oil. $[\alpha]_D^{20}$ = +42.6 (*c* = 0.9, $CHCl_3$). IR (film): ṽ = 2953, 2929, 2857, 1753, 1471, 1460, 1388, 1363, 1249, 1224, 1153, 1103, 1071, 1038, 973, 928, 836, 774, 732, 667 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.00 (s, 3 H, Me-Si), 0.06 (s, 3 H, Me-Si), 0.77 (s, 3 H, Me18′), 0.82 (m, 1 H, H14′), 0.87 (s, 9 H, *t*Bu), 0.90 (m, 1 H, H12′), 1.07 (td, *J* = 3.8, 12.7 Hz, 1 H, H1), 1.20 (s, 3 H, Me14), 1.22 (m, 2 H, H15′, H11′), 1.34 (dd, *J* = 3.2, 13.6 Hz, 1 H, H16′), 1.44 (td, *J* = 3.4, 13.0 Hz, 1 H, H7′), 1.50 (m, 1 H, H11′), 1.58 (m, 2 H, H3, H15′), 1.67 (m, 1 H, H2), 1.70 (td, *J* = 2.6, 11.1 Hz, 1 H, H12′), 1.85 (td, *J* = 3.3, 12.4 Hz, 1 H, H16′), 1.98 (dd, *J* = 6.1, 14.2 Hz, 1 H, H9), 2.05 (s, 3 H, *Me*C=O), 2.25 (d, *J* = 14.2 Hz, 1 H, H9), 3.29 (s, 3 H, C*H*$_3$O-CH$_2$O), 3.41 (s, 3 H, C*H*$_3$O-CH$_2$O), 3.47, (t, *J* = 8.2 Hz, 1 H, H17′), 3.77 (s, 1 H, H6), 4.50 (dd, *J* = 2.4, 3.4 Hz, 1 H, H4), 4.57 (ABq, *J* = 6.7 Hz, 2 H, OC*H*$_2$-OCH$_3$), 4.78 and 4.87 (ABq, *J* = 6.8 Hz, 2 H, OC*H*$_2$-OCH$_3$), 5.33 (d, *J* = 6.1 Hz, 1 H, H8), 6.29 (s, 1 H, H7) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = –2.8 (Me-Si), 0.0 (Me-Si), 14.2 (C18′), 18.4 (C14), 20.2 (C$_q$-*t*Bu), 23.9 (Me), 24.2 (C11′), 25.2 (C15′), 28.7 (3 C, *t*Bu), 30.6 (C12′), 31.4 (C2), 35.4 (C3), 40.1 (C16′), 45.6 (C10), 46.4 (C13), 48.4 (C1), 52.8 (C9), 54.5 (C14′), 57.5 (*C*H$_3$O-CH$_2$O), 58.6 (*C*H$_3$O-CH$_2$O), 69.9 (C4), 77.9 (C6), 88.4 (C5), 88.9 (C17′), 96.0 (C7), 98.0, 101.2 (C8), 101.7, 171.5 ppm. MS (ESI+, MeOH): *m*/*z* (%) = 621.3 (100) [M + Na]$^+$. HRMS (ESI+, MeOH): calcd. for $C_{31}H_{54}O_8NaSi$ 621.3435; found 621.3447. $C_{31}H_{54}O_8Si$ (598.35): calcd. C 62.18, H 9.09; found C 62.22, H 9.25. To a stirred solution of **16** (188 mg, 0.31 mmol) in a mixture of methanol (18 mL) and water (1.5 mL) was added potassium carbonate (434.2 mg, 3.1 mmol). The resulting mixture was stirred at room temperature for 2 h. After removing solvents without heating, dilution with EtOAc, usual workup, and chromatography on silica gel (heptane/EtOAc, 4:1) **17** (148.5 mg, 86%) was obtained. Colorless oil. $[\alpha]_D^{20}$ = 49.7 (*c* = 1.1, $CHCl_3$). IR (film): ṽ = 3734, 2951, 1789, 1699, 1658, 1558, 1506, 1472, 1250, 1205, 1149, 1066, 1044, 945, 917, 836, 777, 668 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.00 (s, 3 H, Me-Si), 0.06 (s, 3 H, Me-Si), 0.76 (s, 3 H, Me18′), 0.82 (m, 1 H, H14′), 0.88 (s, 9 H, *t*Bu), 0.92 (m, 1 H, H12′), 0.97 (m, 1 H, H1), 1.14 (s, 3 H, Me14), 1.20 (m, 2 H, H15′, H11′), 1.35 (m, 2 H, H16′, H3), 1.52 (m, 1 H, H11′), 1.60 (m, 2 H, H3, H15′), 1.62 (m, 1 H, H2), 1.70 (m, 1 H, H12′), 1.95 (m, 1 H, H16′), 2.50 and 2.28 (ABq, *J* = 17.6 Hz, 2 H, 2 H9), 3.23 (s, 3 H, C*H*$_3$O-CH$_2$O), 3.34 (s, 3 H, C*H*$_3$O-CH$_2$O), 3.40, (t, *J* = 8.5 Hz, 1 H, H17′), 3.47, (dd, *J* = 4.0, 8.8 Hz, 1 H, OH), 3.72 (ddd, *J* = 4.2, 6.1, 12.0 Hz, 1 H, H7), 3.90, (dd, *J* = 1.8, 6.6 Hz, 1 H, H6), 3.98, (td, *J* = 2.5, 11.1 Hz, 1 H, H4), 4.19 (dd, *J* = 2.9, 6.0 Hz, 1 H, H6), 4.50 (ABq, *J* = 6.6 Hz, 2 H, OC*H*$_2$-OCH$_3$), 4.57 and 4.72 (ABq, *J* = 6.9 Hz, 2 H, OC*H*$_2$-OCH$_3$) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = –5.1 (Me-Si), –3.7 (Me-Si), 11.8 (C18′), 15.6 (C14), 18.1 (C$_q$-*t*Bu), 22.1 (C11′), 23.1 (C15′), 25.9 (3 C, *t*Bu), 28.0 (C12′), 29.2 (C2), 31.8 (C3), 37.1 (C16′), 43.1 (C10), 43.4 (C13′), 44.7 (C9), 48.7 (C1), 50.2 (C14′), 55.1 (*C*H$_3$-OCH$_2$O), 56.1 (*C*H$_3$-OCH$_2$O), 62.7 (C4), 69.8 (C), 86.2 (C6), 86.9 (C17′), 91.1 (C5), 96.0 (O*C*H$_2$-OCH$_3$), 98.2 (O*C*H$_2$-OCH$_3$), 176.2 (C8) ppm. MS (ESI+, MeOH): *m*/*z* (%) = 579.3 (100) [M + Na]$^+$. HRMS (ESI+, MeOH): calcd. for $C_{29}H_{52}O_8NaSi$ 579.3329; found 579.3316. $C_{29}H_{52}O_8Si$ (556.34): calcd. C 62.56, H 9.41; found C 62.78, H 9.46.

Preparation of Epoxides 5f and 14d and Methyl Carbinol 5e through Alteration of the Configuration at C4: To a solution of sodium hydride (31.2 mg, 1.3 mmol) and trimethylsulfonuim iodide (106.5 mg, 0.52 mmol) in DMSO (0.6 mL) was added dropwise a solution of steroidal ketone **5c** (100 mg, 0.26 mmol) in THF/DMSO (1:1, 1.2 mL) at 25 °C. The reaction mixture was stirred at the same temperature for 12 h. Then it was hydrolyzed with water (3 mL) and extracted with EtOAc (4 × 5 mL). The organic layer was washed with water (5 × 2 mL), dried with anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by column chromatography (heptane/EtOAc, 4:1) to give **5f** (82 mg, 81%). Colorless oil. $[\alpha]_D^{20}$ = +35 (*c* = 1.5, $CHCl_3$). IR (film): ṽ = 2971, 2945, 2905, 2359, 1633, 1456, 1377, 1388, 1360, 1249, 1216, 1203, 1144, 1074, 1086, 1074, 902, 877, 823, 755 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.73 (s, 3 H, Me1′8), 0.96 (m, 1 H), 1.04 (dd, *J* = 4.7, 13.1 Hz, 1 H), 1.11 (s, 9 H, *t*Bu), 1.14 (s, 3 H, Me14), 1.24 (m, 3 H), 1.39 (m, 1 H), 1.46 (m, 3 H), 1.66 (td, *J* = 4.0, 11.3 Hz, 1 H), 1.82 (m, 3 H), 1.90 (d, *J* = 14.2 Hz, 1 H, H9), 2.23 (dd, *J* = 5.6, 14.2 Hz, 1 H, H9), 2.46 (d, *J* = 4.6 Hz, 1 H, H15), 2.82 (d, *J* = 4.6 Hz, 1 H, H15′), 3.35 (t, *J* = 8.3 Hz, 1 H, H17′), 4.83 (d, *J* = 6.7 Hz, 1 H, H6), 5.60 (d, *J* = 5.6 Hz, 1 H, H8), 6.22 (d, *J* = 6.1 Hz, 1 H, H7) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 11.6 (C18′), 13.8 (C14), 21.6 (C11′), 23.5 (C15′), 28.7 (3 C, *t*Bu), 31.2 (C3), 33.3 (C8′), 34.3 (C16′), 37.2 (C12′), 42.7 (C13′), 47.5 (C9), 47.6 (C1), 48.2 (C15), 50.6 (C4), 55.4 (C13′), 55.9 (C10), 72.1 (C$_q$-*t*Bu), 80.6 (C17′), 84.2 (C5), 100.1 (C8), 105.0 (C6), 140.7 (C7) ppm. MS (ESI+, MeOH): *m*/*z* (%) = 390.3 (100) [M + Na]$^+$. HRMS (ESI+, MeOH): calcd. for $C_{24}H_{38}O_4Na$ 390.2692; found 390.2678. $C_{24}H_{36}O_4$ (388.26): calcd. C 74.19, H 9.34; found C 72.75, H 9.48. A solution of potassium *tert*-butoxide (4.88 g, 43.5 mmol) in dry toluene (5 mL) was stirred under an atmosphere of argon at room temperature and to this solution was added methyltriphenylphosphonium bromide (15.56 g, 43.5 mmol). The resulting bright yellow solution was stirred for 1 h and then cooled to 0 °C before ketone **5c** (2.7 g, 7.26 mmol) was added in dry toluene (5 mL). The ice bath was removed, and the solution was stirred at room temperature while the reaction progress was monitored by TLC. After 4 h stirring, the reaction mixture was diluted with heptane and worked up as usual. Rapid filtration through silica gel (heptane/EtOAc, 4:1) afforded **5d** (2.11 g, 78%). Colorless oil. $[\alpha]_D^{20}$ = +50.4 (*c* = 0.95, $CHCl_3$). IR (film): ṽ = 2971, 2928, 2871, 1737, 1628, 1446, 1388, 1375, 1361, 1215, 1206, 1142, 1105, 1090, 1073, 1028, 1000, 912, 875, 825, 800, 749, 666 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.72 (s, 3 H, Me14), 0.90 (m, 1 H, H15′), 1.01 (s, 3 H, Me14), 1.13 (s, 9 H, *t*Bu), 1.26 (m, 3 H, H11′, H14′,

H15′), 1.38 (m, 3 H, H12′, H1, H16′), 1.45 (m, 1 H, H16′), 1.64 (ddd, *J* = 2.8, 7.1, 9.1 Hz, 1 H, H11′), 1.76 (td, *J* = 2.9, 12.5 Hz, 1 H, H12′), 1.87 (m, 1 H, H8′), 1.95 (dd, *J* = 9.8, 12.9 Hz, 1 H, H1′), 2.07 (dd, *J* = 2.9, 11.4 Hz, 1 H, H3), 2.25 (m, 1 H, H3), 2.26 (td, *J* = 5.8, 13.9 Hz, 1 H), 3.38, (t, *J* = 8.2 Hz, 1 H, H17′), 5.08 (s, 2 H, 2 H15), 5.26 (d, *J* = 6.3 Hz, 1 H, H6), 5.64 (d, *J* = 5.6 Hz, 1 H, H8), 6.30 (d, *J* = 6.3 Hz, 1 H, H7) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 11.7 (C18′), 13.3 (C14), 21.6 5 (C11′), 23.6 (C15′), 28.7 (3 C, *t*Bu), 31.2 (C3), 36.7 (C16′), 37.2 (C12′), 37.5 (C8′), 42.7 (C10), 47.5 (C1), 47.9 (C9), 50.7 (C14′), 56.9 (C13′), 72.2 (C_q-*t*Bu), 80.1 (C17′), 84.1 (C5), 100.2 (C8), 107.0 (C6), 113.9 (C15), 139.8 (C7), 144.5 (C4) ppm. MS (ESI+, MeOH): *m*/*z* (%) = 395.2 (100) $[M + Na]^+$. HRMS (ESI+, MeOH): calcd. for $C_{24}H_{36}O_3Na$ 395.2562; found 395.2555. $C_{23}H_{34}O_3$ (372.27): calcd. C 77.38, H 9.74; found C 76.83, H 9.56. *m*-CPBA-mediated epoxidation of substrate **5d** (210 mg, 0.56 mmol) was carried out by using the general procedure (3 h, see the Supporting Information) to give, after SiO_2 flash column chromatography (heptane/EtOAc, 4:1), **14d** (204 mg, 65%). Colorless oil. $[\alpha]_D^{20}$ = +24.0 (*c* = 0.88, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3374, 3018, 2972, 2358, 1731, 1576, 1426, 1362, 1251, 1215, 1057, 916, 743, 667 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.75 (s, 3 H, Me18′), 0.88 (m, 3 H), 1.12 (s, 9 H, *t*Bu), 1.25 (m, 2 H), 1.31 (s, 3 H, Me-14), 1.46 (m, 3 H), 1.51 (m, 2 H), 1.82 (td, *J* = 3.8, 12.6 Hz, 1 H, H16), 2.06 (m, 1 H), 2.18 (dd, *J* = 6.3, 14.6 Hz, 1 H, H1), 2.55 (d, *J* = 14.6 Hz, 1 H, H1), 2.79 (d, *J* = 3.2 Hz, 1 H, H15), 3.24 (t, *J* = 3.2 Hz, 1 H, H15), 3.38 (d, *J* = 8.1 Hz, 1 H, H17′), 4.02 (s, 1 H, H6), 5.44 (s, 1 H, OH), 5.64 (d, *J* = 6.3 Hz, 1 H, H8), 6.13 (s, 1 H, H7), 7.42 (t, *J* = 7.5 Hz, 1 H), 7.57 (td, *J* = 1.4, 8.3 Hz, 1 H), 7.89 (td, *J* = 1.7, 7.8 Hz, 1 H), 7.90 (d, *J* = 1.7 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 11.7 (C18′), 14.6 (C14), 21.6 (C11′), 23.4 (C15′), 28.7 (3 C, *t*Bu), 31.2 (C3), 35.6 (C16′), 36.0 (C8′), 37.1 (C12′), 42.6 (C13′), 45.0 (C9), 49.1 (C10), 50.2 (C1), 50.7 (C15), 52.4 (C14′), 62.3 (C4), 68.7 (C6), 72.3 (C_q-*t*Bu), 80.3 (C17′), 84.6 (C5), 96.4 (C8), 100.6 (C7), 127.7, 129.7, 130.0, 133.2, 133.5, 134.8, 163.5 ppm. MS (ESI+, MeOH): *m*/*z* (%) = 583.2 (100) $[M + Na]^+$. HRMS (ESI+, MeOH): calcd. for $C_{31}H_{41}ClO_7Na$ 583.2439; found 583.2438. $C_{31}H_{41}ClO_7$ (560.25): calcd. C 66.36, H 7.37; found C 68.29, H 8.17. To a solution of ketone **5c** (606 mg, 1.62 mmol) in THF (7 mL) was added methyllithium (1.6 M in ether, 16.2 mmol) at –78 °C, and the mixture was stirred for 45 min under an atmosphere of argon. The reaction mixture was poured into saturated aqueous solution of NH_4Cl at 0 °C, then extracted with EtOAc, washed with saturated aqueous solution of $NaHCO_3$, worked up as usual, and chromatographed on SiO_2 (heptane/EtOAc, 1:1) to give carbinol **5e** (512 mg, 81%) as a single diastereomer. Colorless oil. $[\alpha]_D^{20}$ = +14.6 (*c* = 0.6, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3508, 2969, 2928, 2868, 2359, 2250, 1632, 1447, 1367, 1370, 1361, 1251, 1202, 1193, 1084, 1099, 995, 928, 906, 884, 729, 647 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.73 (s, 3 H, Me18′), 0.94 (m, 2 H), 1.02 (dd, *J* = 4.4, 10.6 Hz, 1 H), 1.06 (dd, *J* = 4.4, 10.9 Hz, 1 H), 1.11 (s, 9 H, *t*Bu), 1.15 (s, 3 H, Me14), 1.25 (s, 3 H, Me15), 1.37 (m, 3 H), 1.48 (dd, *J* = 3.4, 13.0 Hz, 1 H), 1.57 (m, 2 H), 1.76 (td, *J* = 3.2, 12.5 Hz, 1 H), 1.86 (m, 2 H, H3, H9), 2.18 (dd, *J* = 6.0, 14.0 Hz, 1 H, H9), 3.35 (t, *J* = 8.3 Hz, 1 H, H17′), 5.27 (d, *J* = 6.1 Hz, 1 H, H6), 5.48 (d, *J* = 5.6 Hz, 1 H, H8), 6.29 (d, *J* = 6.1 Hz, 1 H, H7) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 11.7 (C18′), 15.4 (C14), 21.3 (C11′), 23.7 (C15′), 26.7 (C14′), 28.7 (3 C, *t*Bu), 31.2 (C3), 31.3 (C8′), 37.3 (C16′), 40.7 (C12′), 42.7 (C13′), 47.5 (C1), 48.1 (C9), 50.2 (C14′), 54.5 (C10), 71.1 (C_q-*t*Bu), 72.0 (C4), 80.8 (C17′), 85.2 (C5), 98.9 (C8), 107.2 (C6), 140.2 (C7) ppm. MS (ESI+, MeOH): *m*/*z* (%) = 390.3 (100) $[M + Na]^+$. HRMS (ESI+, MeOH): calcd. for $C_{24}H_{38}O_4Na$ 390.2692; found 390.2678.

CCDC-772959 (for **2d**), -772958 (for **9a**), -772956 (for **10a**), and -772957 (for **14f**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Supporting Information (see footnote on the first page of this article): Experimental procedures for the reactions described herein and characterization data for all new compounds.

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[12] The numbering system for agarofurans as in ref.[3a] will be used throughout the paper for all compounds, including hybrids.
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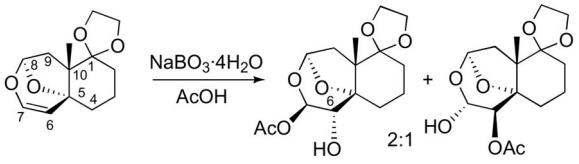
[14] No substituent other than hydrogen at C4 leads to a mixture:



[15] The site-selective disproportionation of the Cannizzaro oxidoreduction is consistent with direct hydride shift on lactol–aldehyde **ii**. Conversion of **10a** into MOM-protected **11a** preceded basic treatment because a free hydroxy group at C6 was susceptible to react with the resulting lactone carbonyl.
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[18] Carrying out TBS protection at 60 °C for 4 h forced the strain releasing nucleophilic opening of the epoxide ring.
[19] It seems reasonable that proximal ring substituents in domino substrate **5** might control approach of the reagent (the angular methyl group at C10) as well as create repulsive nonbonding interactions (the C4 substituents) within the intermediates and encourage conditions for stereoselective epoxide formation and regioselective opening.

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