Chromium-Mediated Dearomatization: Application to the Synthesis of Racemic 15-Acetoxytubipofuran and Asymmetric Synthesis of Both Enantiomers

by **E. Peter Kündig***, **Mundruppady S. Laxmisha**, **Rita Cannas**, **Sylvie Tchertchian**, and **Liu Ronggang**

Department of Organic Chemistry, University of Geneva, 30, Quai Ernest Ansermet, CH-1211 Geneva 4 (e-mail: peter.kundig@chiorg.unige.ch)

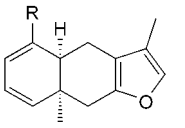
An efficient dearomatization process of [Cr(arene)$(CO)_3$] complexes initiated by a nucleophilic acetaldehyde equivalent is detailed. It generates in a one-pot reaction three C–C bonds and two stereogenic centers. This process allowed a rapid assembly of a *cis*-decalin ring system incorporating a homoannular diene unit in just two steps starting from aromatic precursors (*Scheme 2*). The method was applied to the total synthesis of the eudesmane-type marine furanosesquiterpene (±)-15-acetoxytubipofuran (**2**). Two routes were successfully used to synthesize the γ-lactone precursor of the furan ring. The key step in the first approach was a Pd-catalyzed allylic substitution (*Scheme 3*), while in the second approach, an *Eschenmoser–Claisen* rearrangement was highly successful (*Scheme 4*). The Pd-catalyzed allylic substitution could be directed to give either the (normal) product with overall retention as major diastereoisomer or the unusual product with inversion of configuration (see *Table*). For the synthesis of the (–)-enantiomer (*R,R*)-**2** of 15-acetoxytubipofuran, an enantioselective dearomatization in the presence of a chiral diether ligand was implemented (*Scheme 7*), while the (+)-enantiomer (*S,S*)-**2** was obtained *via* a diastereoselective dearomatization of an arene-bound chiral imine auxiliary (*Scheme 8*). Chiroptical data suggest that a revision of the previously assigned absolute configuration of the natural product is required.

Introduction. – Tricarbonylchromium-mediated dearomatization provides an efficient access to polysubstituted cyclohexadienes [1]. Up to three C-substituents can be added across an arene double bond in a one-pot procedure in a regio- and stereoselective manner by a sequential nucleophilic/electrophilic addition or by a nucleophilic addition followed by an acylation/alkylation sequence [2]. This dearomatization method has seen considerable development, with recent efforts mainly directed towards asymmetric variants of this reaction to give enantiomerically enriched products. Four different asymmetric methods have been developed: asymmetric induction with complexes of arenes bearing a chiral auxiliary as substituent [3], use of arene complexes possessing planar chirality [4], use of prochiral complexes with chiral nucleophiles [5], and use of complexes containing a chiral ligand at the chromium atom [6]. Benchmark enantio- and diastereoselectivities have been obtained in dearomatizations with these methods. In all but the last method, asymmetric induction takes place during the nucleophilic addition step. The third method offers an enantioselective variant in that chirality can be centered on an external ligand rather than on the nucleophile itself, and first results of the use of substoichiometric quantities of chiral information have been realized [7].

In all of the dearomatization processes mentioned above, the products possess a homoannular cyclohexadiene moiety. This subunit embedded in a *cis*-decalin ring

system is a characteristic structural feature of many eudesmane-type marine furanosesquiterpenes, and thus a dearomatization process would appear to be ideal for the synthesis of this class of natural products. We here report the total synthesis of 15-acetoxytubipofuran in both racemic and enantiomerically pure form, in which the chromium-mediated dearomatization serves as the key transformation. A preliminary report of part of this work has been published [8].

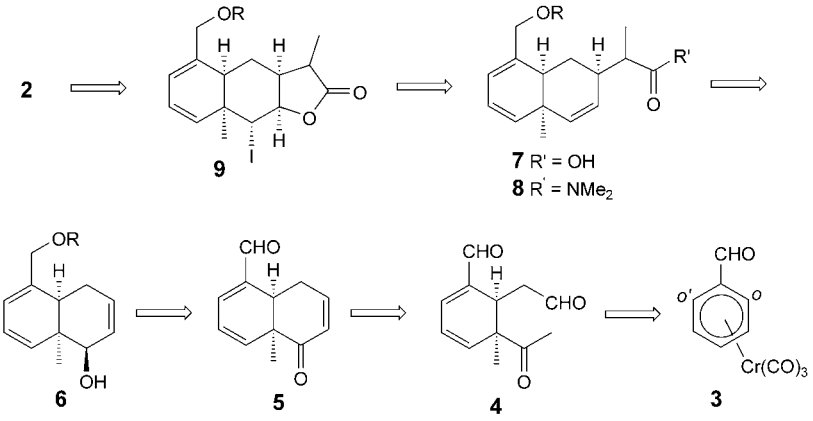
The furanosesquiterpenes tubipofuran (**1**) and 15-acetoxytubipofuran (**2**) were isolated from Japanese stolonifer *Tubipora musica Linnaeus* in 1986 and were shown to be eudesmane-type marine sesquiterpenoids having a *cis*-decalin ring with a homoannular 1,3-diene unit [9]. The compounds show ichtiotoxicity toward killifish (*Orizias latipes*), and 15-acetoxytubipofuran (**2**) shows cytotoxicity against B-16 melanoma cells *in vitro* (IC_{50} 33 μg/ml). On the basis of the diene helicity rule, the (4a*S*,8a*R*) absolute configuration was originally assigned to (+)-**1**, but the work of *Pedro* and co-workers, who converted santonin into tubipofuran, showed that this has to be revised and that tubipofuran (+)-**1** has the (4a*R*,8a*S*) absolute configuration as shown in structure **1** [10]. A synthesis of racemic tubipofurans was reported by *Kanematsu* and co-workers in 1994 [11].



1 R = Me
2 R = $AcOCH_2$

The salient features of our synthetic strategy are shown in *Scheme 1*. In terms of the synthesis end game, it was envisioned that iodolactone **9**, obtained by the iodolactonization of acid **7** or amide **8**, could be processed to deliver the target compound **2** by straightforward functional-group manipulations. Compounds **7** and **8** were seen to be accessible from allylic alcohol **6** *via* a Pd-catalyzed allylic substitution reaction or *via* a *Claisen* rearrangement. Alcohol **6** can in turn be obtained from the bicyclic enone **5**, itself accessible from keto aldehyde **4** by an intramolecular aldol condensation. Hence, at the outset of our investigation, the key issue that needed to be addressed was the nucleophilic addition of an acetaldehyde unit (or equivalent) to the *ortho* position of [Cr(benzaldehyde)$(CO)_3$] (**3**) (or a derivative thereof) followed by a regioselective and stereoselective acylation/alkylation at C(5) to give diene **4**. Enantiomerically pure **2** was envisioned to be available by an enantioselective nucleophilic addition to complex **3** (or a derivative thereof) in the presence of a chiral ligand or by a diastereoselective nucleophilic addition in the presence of an arene-bound chiral auxiliary, followed by a diastereoselective acylation/alkylation sequence. The notable features of this synthetic plan are: *a*) the generation of three C–C bonds and two stereogenic centers in a configurationally defined fashion in a one-pot operation, and *b*) a rapid construction of the *cis*-decalin ring system featuring a homoannular cyclohexadiene unit as required in **5**, in just two steps from an aromatic precursor. To study the feasibility of the projected synthesis, a synthesis of racemic **2** was undertaken first. Its success then encouraged us to carry out asymmetric syntheses of both enantiomers.

Scheme 1. *Strategy for the Synthesis of 15-Acetoxytubipofuran* (**2**)

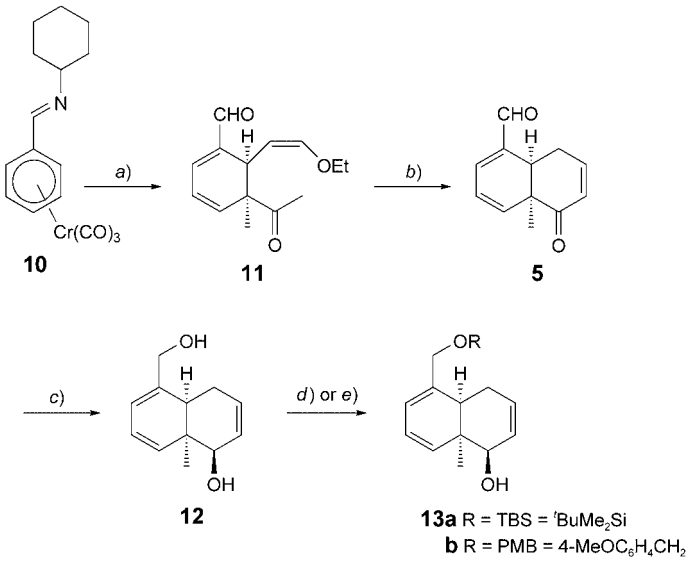


Results and Discussion. – As our synthetic plan required the addition of a nucleophilic acetaldehyde unit or its equivalent to the benzaldehyde complex **3**, we first sought to investigate methods to achieve this transformation. We selected the benzaldimine complex **10** [12], which had been used successfully as substrate in previous dearomatization studies [1], and which had shown excellent *ortho*-selectivity in both nucleophilic addition reactions [12] and in lithiation reactions [13]. For the nucleophilic addition, [(1*Z*)-2-ethoxyethenyl]lithium was chosen as the nucleophilic acetaldehyde equivalent [14]. Thus, *ortho*-addition of [(1*Z*)-2-ethoxyethenyl]lithium to imine complex **10** followed by an acylation/alkylation sequence and imine hydrolysis gave aldehyde **11** with the correct relative configuration. Enol ether hydrolysis and intramolecular aldol condensation were performed in a one-pot reaction under acidic conditions to afford enone **5** with the anticipated *cis*-decalin skeleton. This method thus gave a very rapid access to **5** possessing the homoannular diene moiety in just two steps from the aromatic precursor complex **10**. Reduction of enone **5** under *Luche* conditions [15] furnished diol **12** as a single diastereoisomer by hydride addition to the ketone from the more accessible, convex face of the molecule. To enable a regioselective transformation of the secondary allylic alcohol, the primary hydroxy group in **12** was protected by treatment with Et_3N/DMAP/^{t}BuMe$_2$SiCl in DMF at 0° to give the silyloxy derivative **13a** or with NaH/4-MeO-$C_6H_4CH_2I$ in DMF at −50° to give the methoxybenzyloxy derivative **13b** in good yield (*Scheme 2*).

Pd-Catalyzed Allylic Substitution. With allylic alcohols **13a**,**b** in hand, we began to explore efficient means of introducing a C_3 side chain required for the projected iodolactonization. Among the more-attractive options was a sequence involving a Pd-catalyzed allylic substitution reaction of the allylic acetate **14** or carbonate **15** with dimethyl methylmalonate anion (*Scheme 3*).

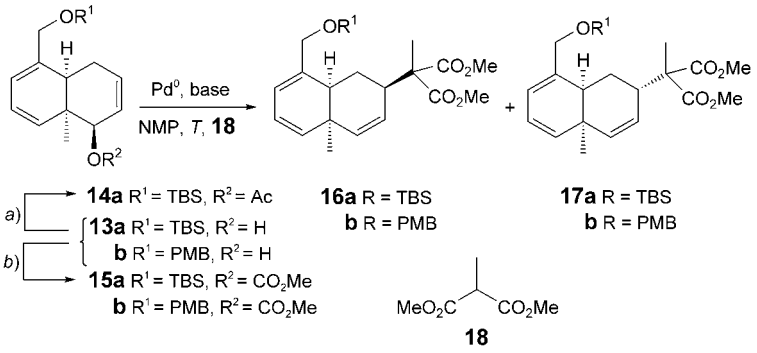
The acetate **14a** and carbonates **15a** and **15b** were obtained by treatment of **13a**,**b** with Ac_2O/pyridine or methyl carbonochloridate/pyridine/DMAP, respectively. Initial reactions were carried out with the products **14a** and **15a** containing the silyl protecting group. Subsequently we switched to the methoxybenzyl-protected alcohol **15b** because

Scheme 2. *Synthesis of the* cis-*Fused Bicyclic Intermediate* **13**.



a) 1) (1*Z*)-1-Bromo-2-ethoxyethene, ^{t}BuLi, $-78°$, Et_2O/THF; 2) MeI, hexamethylphosphoric triamide (HMPA), CO, $-78°$ to r.t., 3) 2M NaOEt, MeI, $-78°$ to r.t., 66%. *b*) 2M HCl, THF, reflux; 89%. *c*) $CeCl_3 \cdot 7H_2O$, $NaBH_4$, MeOH, 0°; 98%. *d*) Et_3N, *N*,*N*-dimethylpyridin-4-amine (DMAP), ^{t}BuMe$_2$SiCl, DMF, 0°; 94%. *e*) NaH, DMF, $-60°$, then 4-MeOC$_6$H$_4$CH$_2$I, $-50°$; 88%.

Scheme 3. *Diastereoselectivities in the Pd-Catalyzed Allylic Alkylation*



TBS = ^{t}BuMe$_2$Si, PMB = 4-MeOC$_6$H$_4$CH$_2$, NMP = 1-methylpyrrolidin-2-one

a) Ac_2O, pyridine, DMAP, CH_2Cl_2, 0°; 91 %. *b*) $ClCO_2Me$, pyridine, DMAP, CH_2Cl_2, 0°; 95%.

of the higher stability of this protecting group under conditions of hydrolysis of diester **16**. The Pd-catalyzed allylic substitution reaction was studied in detail with different Pd^0 catalysts and the anion of dimethyl methylmalonate (**18**) as the nucleophile (*Table*). When the reaction was carried out with acetate **14a** and $[Pd(PPh_3)_4]$ as catalyst, a 7:3 mixture of diastereoisomers **16a** and **17a** was obtained favoring the normal allylic

substitution product **16a** (*Entry 1*). This low diastereoselectivity was also found when the reaction was carried out with carbonates **15a** and **15b** where the reaction temperature could be lowered to room temperature (*Entries 2* and *3*). The reaction of **15b** was also performed in the absence of external base with $[Pd(PPh_3)_4]$ as the catalyst; the reaction was slower in this case but heating to 60° solved this problem. Remarkably, diastereoselectivity was reversed under these conditions affording **16b** and **17b** in a 15:85 ratio (*Entry 4*). Reflecting on the origin of this change of selectivity (see below), we switched to $[Pd(dppe)_2]$ as catalyst (dppe = ethane-1,2-diylbis[diphenylphosphine]), and this afforded the normal substitution product with high diastereoselectivity both in the presence and absence of an added external base (*Entries 5* and *6*). The catalyst incorporating the bidentate ligand dppe thus largely suppressed the formation of **17b** in this substitution reaction.

Table. *Diastereoselectivities in the Pd-Catalyzed Allylic Alkylation.*

Entry	R^2	*T* [°]	Base	Pd^0	**16**/**17**[a])	Yield [%]
1	Ac (**14a**)	60	NaH	$[Pd(PPh_3)_4]$	70:30[b])	84
2	CO_2Me (**15a**)	25	NaH	$[Pd(PPh_3)_4]$	70:30[c])	91
3	CO_2Me (**15b**)	25	NaH	$[Pd(PPh_3)_4]$	75:25[c])	67
4	CO_2Me (**15b**)	60	none	$[Pd(PPh_3)_4]$	15:85[d])	61
5	CO_2Me (**15b**)	25	NaH	$[Pd(dppe)_2]$	>98:>2[e])	99
6	CO_2Me (**15b**)	50	none	$[Pd(dppe)_2]$	92:8[f])	75

[a]) *Entries 1* and *2:* products **16a**/**17a**; *Entries 3–6:* products **16b**/**17b**; the reactions were carried out under the conditions given in [a])–[f]); NMP = 1-methylpyrrolidin-2-one, dppe = ethane-1,2-diylbis[diphenylphosphine]. [b]) **14a** (1.0 equiv.), $[Pd(PPh_3)_4]$ (0.1 equiv.), NaH (3.0 equiv.), **18** (3.0 equiv.) in NMP; products **16a**/**17a**. [c]) **15a** or **15b** (1.0 equiv.), $[Pd(PPh_3)_4]$ (0.1 equiv.), NaH (4.0 equiv.), **18** (4.0 equiv.) in NMP. [d]) **15b** (1.0 equiv.), $[Pd(PPh_3)_4]$ (0.1 equiv.), **18** (3.0 equiv.) in NMP; products **16b**/**17b**. [e]) **15b** (1.0 equiv.), $[Pd(dppe)_2]$ (0.1 equiv.), NaH (3.0 equiv.), **18** (3.0 equiv.) in NMP; product **16b**. [f]) **15b** (1.0 equiv.), $[Pd(dppe)_2]$ (0.1 equiv.), **18** (3.0 equiv.) in NMP; products **16b**/**17b**.

Oxidative addition of phosphinepalladium(0) complexes to allylic substrates to give π-allyl complexes has been established to proceed with inversion of configuration after prior coordination of the metal to the C=C bond [16]. It has also been shown that this is a reversible reaction for allyl acetates and even for allyl carbonates [17]. Subsequent nucleophilic attack of stabilized carbanions on the (π-allyl)palladium complex occurs on the face opposite to the metal and leads to the product with overall retention of configuration. Erosion of stereospecificity in this reaction (usually $<10\%$ when the nucleophile is a carbanion) has been attributed to several competing reaction pathways [18]. With cyclic substrates, an important pathway is the Pd^0-catalyzed isomerization of the intermediate π-allyl complex by a mechanism involving nucleophilic *trans* attack by the $[Pd^0(\text{phosphine})]$ complex fragment (*Fig.*) [17–20][1]).

In the examples studied, with both **14** and **15**, the normal Pd-catalyzed substitution by the anion of **18** (overall retention) giving **16** is the major pathway when the reaction is performed in the presence of an external base (*Table*, *Entries 1–3*) though lower diastereoselectivities are found than those usually observed. This is readily attributed to the requirement that the carbanion must approach from the concave side of the

[1]) First suggested in [19].

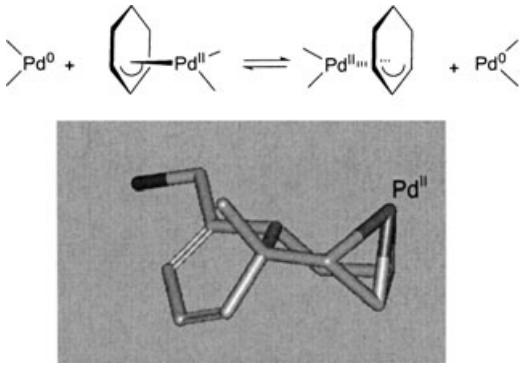


Figure. *Pd-Catalyzed isomerization of [Pd(π-allyl)] intermediates and model of the initially formed [Pd(allyl)] complex from the reaction of* **14** *or* **15** *with a Pd⁰ complex.* Phosphine ligands and H-atoms are omitted for clarity.

molecule (*Fig.*). In the absence of an external base, the C-nucleophile concentration in the reaction mixture is low. Under these conditions, the rate of Pd^0-catalyzed isomerization competes successfully with that of carbanion attack. After isomerization, carbanion attack proceeds rapidly from the convex face of the molecule to give **17** as the major product (*Entry 4*). The much higher selectivity observed with $[Pd(dppe)_2]$ (*Entries 5* and *6*) is best explained by the much poorer leaving-group properties of the [Pd(dppe)] fragment compared to $[Pd(PPh_3)_2]$ as documented elegantly in [20–22].

Eschenmoser–Claisen *Rearrangement and Iodolactonization.* In parallel to the Pd-catalyzed substitution reaction, another attractive option for introducing the C_3-side chain involves a *Claisen* rearrangement. No product could be isolated under conditions of the *Johnson–Claisen* rearrangement applied to **13**, presumably due to the sensitivity of the substrate to mild acidic conditions at elevated temperature (mercuric salts or propanoic acid). We therefore turned to the less explored *Eschenmoser–Claisen* rearrangement [23][2]). The advantage of the *Eschenmoser–Claisen* rearrangement in our synthetic sequence is that unlike the *Claisen* and the *Johnson–Claisen* rearrangements, the product can directly participate in the next step, the iodolactonization reaction. In the event, heating a mixture of **13b** and an excess of orthoamide **19** [24] in xylene in a sealed tube furnished amide **20** as a 1:1 mixture of diastereoisomers in nearly quantitative yield (*Scheme 4*). Iodolactonization of **20** with I_2 in THF/H_2O 2:1 was straightforward, giving iodolactone **21** as a 1:1 mixture of diastereoisomers. Iodolactone **21** was found to be identical to that obtained by the iodolactonization of acid **22**, in turn obtained by the hydrolysis and decarboxylation of diester **16b** with NaOH/DMSO. The *Eschenmoser–Claisen* rearrangement offers a distinct advantage over the Pd-catalyzed allylic substitution in that **21** can be obtained in fewer steps from allylic alcohol **13b**.

With a viable method for the introduction of the C_3 side chain in hand, the synthesis was carried on from iodolactone **21**. The next focus in the synthetic sequence was the conversion of the lactone unit in **21** to the corresponding furan. This conversion was

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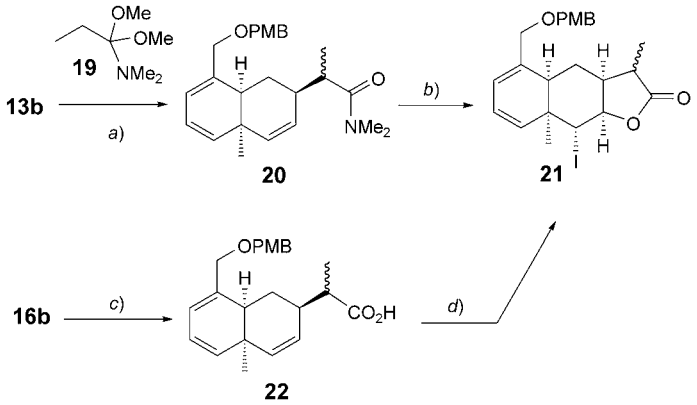
[2]) For some synthetic applications, see [23b,c].

Scheme 4. Eschenmoser–Claisen *Rearrangement and Iodolactonization*

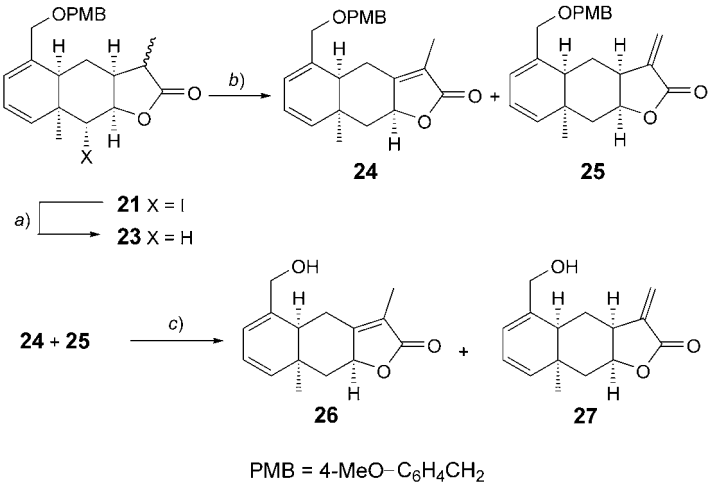


PMB = 4-MeO–$C_6H_4CH_2$

a) **19**, xylene, 150°; 98%. *b*) I_2, THF/H_2O 2:1; 73%. *c*) 6M NaOH, DMSO, 130°; 93%. *d*) I_2, $NaHCO_3$, H_2O, CH_2Cl_2; 94%.

expected to be straightforward from the corresponding butano-4-lactone, taking advantage of the well-known aptitude of diisobutylaluminium hydride (DIBAL) to reduce butano-4-lactones [25]. Toward this end, iodide **21** was reduced under radical conditions with tributylstannane to afford lactone **23** in very good yield (*Scheme 5*). Treatment of lactone **23** with LDA/PhSeCl followed by oxidation and selenoxide

Scheme 5



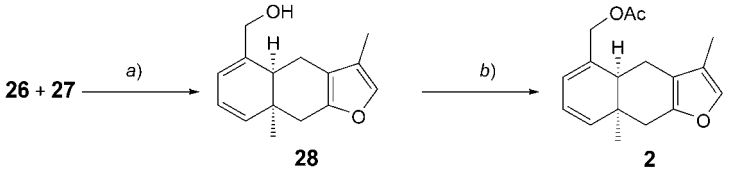
PMB = 4-MeO–$C_6H_4CH_2$

a) Bu_3SnH, 2,2′-azobis[2-methylpropanenitrile] (AIBN), toluene; 91%. *b*) lithium diisopropylamide (LDA), PhSeCl, THF, then H_2O_2, pyridine, CH_2Cl_2; 66%. *c*) 4,5-dichloro-3,6-dioxocyclohexadiene-1,2-dicarbonitrile (DDQ), CH_2Cl_2/H_2O 20:1; 80%.

elimination furnished a mixture of unsaturated lactones **24** and **25** in a 3:2 ratio in a respectable 66% overall yield. Although the projected DIBAL reaction can be performed at this stage of the synthesis, this step was delayed until after the deprotection of the methoxybenzyl group because of the known sensitivity of furan to oxidative methoxybenzyl-deprotection conditions [26]. Consequently, the methoxybenzyl group in **24** and **25** was deprotected with DDQ in wet CH_2Cl_2 [27] to furnish a mixture of alcohols **26** and **27** in a 3:2 ratio.

The stage was now set for the crucial DIBAL-mediated conversion of lactone **26** into furan. Although **26** and **27** were not separable, it was reasoned that **27** would also give the corresponding furan by the DIBAL-mediated reduction followed by C=C bond migration and dehydration. After some experimentation, the best result was obtained by treating the mixture **26**/**27** with 6 equiv. of DIBAL in toluene at $-40°$ followed by workup with AcOH [28]. Under these conditions, furan **28** was obtained in 73% yield (*Scheme 6*). Finally, acetylation of the OH group with Ac_2O and pyridine in the presence of catalytic amounts of DMAP in CH_2Cl_2 gave **2** in high yield. Compound **2** exhibited spectral data fully consistent with those of the literature [9].

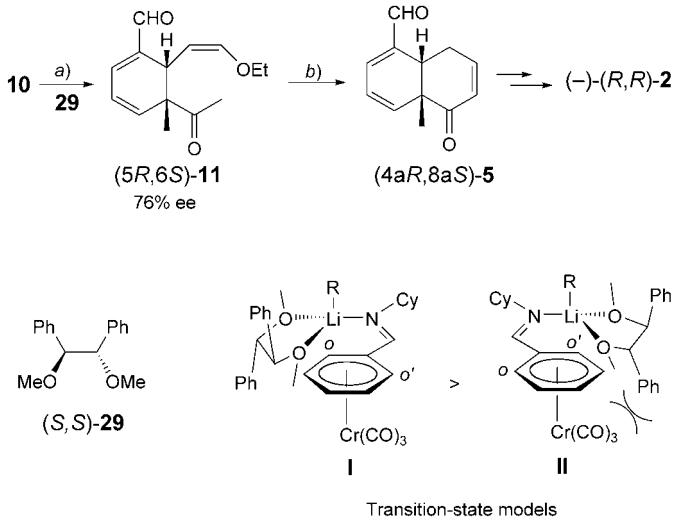
Scheme 6



a) DIBAL, toluene, $-40°$, then AcOH, $-40°$ to r.t.; 73%. *b*) Ac_2O, pyridine, DMAP, CH_2Cl_2, 0°; 93%.

Asymmetric Syntheses of Both Enantiomers of **2**. With a viable synthetic sequence for the target molecule in hand, we began to explore methods for the asymmetric addition of [(1*Z*)-2-ethoxyethenyl]lithium to the imine complex **10**. We first chose an enantioselective nucleophilic addition in the presence of diether (*S*,*S*)-**29**. In our previous study, this chiral ligand had been found to give high asymmetric induction (> 90% ee) in nucleophilic additions of organolithium reagents to **10** in toluene [5]. However, nucleophilic addition of [(1*Z*)-2-ethoxyethenyl]lithium to **10** in the presence of **29** in a mixture of Et_2O and toluene gave (5*R*,6*S*)-**11** in modest 42% yield and 76% ee (*Scheme 7*). The need for Et_2O as solvent in the generation of the organolithium reagent by metal/bromide exchange and the low thermal stability of the nucleophile are at the origin of the erosion of both enantioselectivity and yield. Fortunately, recrystallization of (4a*R*,8a*S*)-**5**, obtained by a one-pot hydrolysis and aldol condensation, furnished a enantiomerically highly enriched product (> 99% ee). The sense of asymmetric induction observed in this reaction is rationalized on the basis of transition-state models for the nucleophilic addition. Of the two transition-state models **I** and **II** corresponding to the addition of the nucleophile to the two enantiotopic *ortho* positions, the preference for addition to the *ortho* rather than the *ortho*′ position is based on steric congestion between the Ph group of the chiral ligand and the $[Cr(CO)_3]$ group in transition state **II**.

Scheme 7



a) 1) (1*Z*)-1-Bromo-2-ethoxyethene, ^{t}BuLi, $-78°$, **29**, Et_2O/toluene, $-78°$ to $-50°$; 2) MeI, HMPA, CO, $-78°$ to r.t.; 3) 2M NaOEt, MeI, $-78°$ to r.t., 42% (one-pot). *b*) 2M HCl, THF, reflux, 89%.

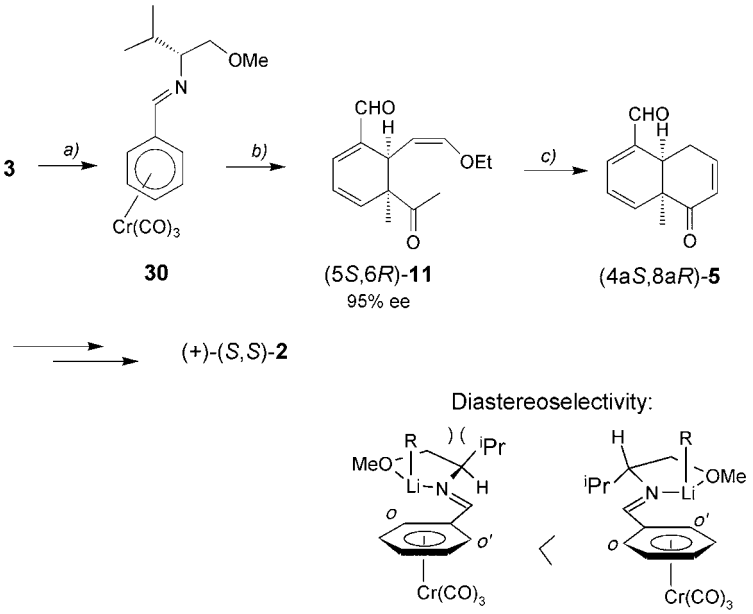
Keto aldehyde (4a*R*,8a*S*)-**5** was converted into (−)-(*R*,*R*)-**2** by employing the same sequence of reactions as described for the synthesis of *rac*-**2**, with the Pd-catalyzed allylic substitution reaction as key step. Compound (*R*,*R*)-**2** showed an $[\alpha]_D^{20}$ value of -120 ($c = 0.653$, $CHCl_3$), while the natural product was previously assigned the (*R*,*R*)-configuration, and its $[\alpha]_D^{20}$ value was reported as $+10.7$ ($c = 0.5$, $CHCl_3$). The CD spectrum of the synthetic sample showed a negative *Cotton* effect at λ_{max} 274 ($\Delta\varepsilon - 3$), opposite to that reported (λ_{max} 270 ($\Delta\varepsilon + 3$)) [9]. As mentioned before, the conversion of santonin into (+)-tubipofuran required a reassignment of the absolute configuration in the natural product [10]. Moreover, the observed $[\alpha]_D^{20}$ value (+33) of tubipofuran was much larger than that reported earlier for the natural product (+5.6), suggesting that the natural product isolated may not have been optically pure. Our synthetic study shows that a parallel situation exists for 15-acetoxytubipofuran and that the absolute configuration assigned initially needs to be revised.

Although the synthesis of (−)-(*R*,*R*)-**2** yielded the enantiomerically enriched form by an enantioselective nucleophilic addition, the moderate induction observed in this reaction offset the intrinsic advantage of this process over a chiral-auxiliary-mediated diastereoselective addition. In an effort to improve the asymmetric induction in the nucleophilic addition and being mindful of the need to synthesize the natural (+)-(*S*,*S*)-**2** for comparison, we investigated a chiral-auxiliary-mediated diastereoselective nucleophilic addition. We employed the valinol-derived benzaldimine complex **30** as starting material for the nucleophilic addition[3]). Complex **30** was prepared by condensation of benzaldehyde complex **3** with D-valinol followed by *in situ* methylation

[3]) For some previous examples on the use of valinol-derived chiral auxiliaries in asymmetric synthesis, see [29].

with NaH/MeI (*Scheme 8*). Diastereoselective nucleophilic addition followed by acylation/alkylation and imine hydrolysis yielded (−)-(5*S*,6*R*)-**11**. Fortunately, both the yield and the enantiomer purity of the product were superior to those obtained by the enantioselective nucleophilic addition described before. In terms of diastereoselection, this result represents a significant improvement over the previously reported diastereoselective addition to arenes bearing chiral imine auxiliaries [3]. A one-pot hydrolysis and aldol condensation of (5*S*,6*R*)-**11** furnished keto aldehyde (4a*S*,8a*R*)-**5**. A single recrystallization afforded enantiomerically highly enriched (+)-**5** (> 99% ee). From here on, the synthesis followed the same route as described for the synthesis of (−)-(*R*,*R*)-**2**, except that the four-step sequence involving formation of carbonate, Pd-catalyzed allylic substitution reaction, hydrolysis/decarboxylation, and lactonization was now replaced by the more efficient two-step *Eschenmoser–Claisen* rearrangement and lactonization sequence. (+)-(*S*,*S*)-**2** showed an $[\alpha]_D^{20}$ value of +100.3 ($c = 0.29$, $CHCl_3$).

Scheme 8. *Highly Diastereoselective Nucleophile Addition/Acylation/Alkylation of* **30**



a) 1) D-Valinol, Et_2O, r.t., 2) NaH, MeI, THF, r.t., 73% (one-pot). *b*) 1) (1*Z*)-1-Bromo-2-ethoxyethene, ^{t}BuLi, −78°; 2) MeI, HMPA, CO, −78° to r.t.; 3) 2M NaOEt, MeI, −78° to r.t.; 53% (one-pot). *c*) 2N HCl, THF, 80°; 89%.

Conclusions. – Through the total synthesis of 15-acetoxytubipofuran (**2**), we illustrated the synthetic utility and demonstrated several new features of the chromium-mediated dearomatization process involving a nucleophilic acetaldehyde equivalent. The synthetic study presented here demonstrates the use of a chiral ligand or an arene-bound chiral auxiliary to efficiently control the absolute, respectively, the relative configuration in nucleophilic addition reactions. The highly asymmetric

induction in the nucleophilic addition to valinol-derived imine complex **30** is a significant advancement of the auxiliary-directed asymmetric dearomatization. The stereochemical issues associated with the diastereoselective Pd-catalyzed allylic substitution reaction with different Pd-catalysts were studied in some detail. The asymmetric synthesis of 15-acetoxytubipofurans (−)-(*R*,*R*)-**2** and (+)-(*S*,*S*,)-**2** detailed in this article suggests that the absolute configuration assigned for the natural product needs to be revised. The synthetic protocols described in this work are useful for the transformation of simple aromatics into enantiomerically highly enriched alicyclic compounds with functionality suitable for their use as building blocks for natural-product synthesis. This is clearly demonstrated by the synthesis of both enantiomers of 15-acetoxytubipofuran.

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Experimental Part

General. $Cr(CO)_6$ was from *Strem Chemicals*. Et_2O and THF were distilled from Na/benzophenone ketyl under N_2, and toluene was distilled over Na under N_2. BuLi (*Fluka*; 1.7M) was titrated before use [30]. D-Valinol was prepared by a literature method [31]. [Cr(η^6-benzaldehyde)$(CO)_3$] (**3**) [12][32] and [Cr{(η^6-benzylidene)-cyclohexylamine}$(CO)_3$] (**10**) [12] were prepared as previously reported. All other chemicals were purchased from *Aldrich* or *Fluka* and were purified following standard literature procedures. Reactions and manipulations involving organometallics were carried out under purified N_2 by using an inert gas/vacuum double manifold and standard *Schlenk* techniques [33]. Flash chromatography (FC) was carried out as described by *Still* (*Merck-60* silica gel) [34]. GC: *Hewlett-Packard 6890* gas chromatograph with FID detection; *Permabond OV-1701-0.25* column (25 m × 0.32 mm i.d.) or chiral *MN-FS-Lipodex-E* column (25 m × 0.25 mm i.d.); t_R in min. HPLC: *Jasco PU-980* chromatograph with a *Jasco UV-975* detector; *Chiralcel OD*, *Chiralcel OD-H*, or *Chiralcel OJ* columns t_R in min. (*Daicel Chemical Industries Ltd.*; 25 cm × 0.46 cm); M.p.: *Büchi 510* apparatus; not corrected. Optical rotation: *Perkin-Elmer 241*, quartz cell (l = 10 cm), high-pressure lamps of sodium (λ 589 nm) and mercury (λ 578 nm). IR: *Perkin-Elmer 1650-FT-IR*; $\tilde{\nu}$ in cm^{-1}. ^{1}H- and ^{13}C-NMR: *Varian XL-200* and *Bruker 400* spectrometer; δ in ppm, J in Hz. HR-MS: *VG7070E* spectrometer (data system 11 250, resoln. 7000); in m/z (rel. int. in % of the base peak). Elemental analyses: *H. Eder*, Service de Microchimie, Section des Sciences Pharmaceutiques, Université de Genève.

*(5*RS*,6*SR*)-5-Acetyl-6-(2-ethoxyethenyl)-5-methylcyclohexa-1,3-diene-1-1carboxaldehyde* (**11**). To a soln. of (1*Z*)-1-bromo-2-ethoxyethene (5.3 ml, 50 mmol) and 3-(*tert*-butyl)-4-hydroxy-5-methylphenyl sulfide (=4,4′-thiobis[2-(*tert*-butyl)-6-methylphenol]; 20 mg) in Et_2O (50 ml) in a 500-ml pressure-resistant flask at −78°, 1.7M ^{t}BuLi in pentane (58.8 ml, 100 mmol) was added dropwise *via* cannula. After stirring at −78° for 1 h, a cold (−78°) soln. of complex **10** (8.0 g, 25 mmol) in THF (125 ml) was transferred *via* cannula. After stirring for 4 h at −78°, MeI (15.5 ml, 250 mmol) and hexamethylphosphoric triamide (HMPA; 44.6 ml, 100 mmol) were added, and 4 bar CO was pressed onto the mixture. The mixture was warmed slowly to r.t. and stirred overnight. Excess CO was vented, and volatiles were evaporated. The residue was dissolved in THF (400 ml), and 2M NaOEt in EtOH (18.7 ml, 37.5 mmol) was added at −78°. After stirring for 15 min, MeI (15.5 ml, 250 mmol) was added, and the soln. was slowly warmed to r.t. over 2 h and stirred for an additional hour. Volatiles were evaporated, and the residue was dissolved in Et_2O and filtered through a short layer of silica gel. Purification by FC (silica gel, pentane/Et_2O 3:1 → 2:1) afforded **11** (3.840 g, 66%). Yellow oil. IR ($CHCl_3$): 1701, 1673, 1206. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.19 (*s*, Me−C(5)); 1.25 (*t*, J = 7.0, *Me*CH_2O); 2.19 (*s*, MeCO); 3.77–3.87 (*m*, H−C(6), C*H*=CHOEt); 4.09–4.18 (*m*, MeC*H*$_2$O); 5.81 (*d*, J = 5.7, H−C(4)); 6.18 (*dd*, J = 9.7, 5.3, H−C(3)); 6.67–6.70 (*m*, H−C(2), CH=C*H*OEt); 9.52 (*s*, CHO). ^{13}C-NMR (100 MHz, $CDCl_3$): 15.3; 21.4; 25.1; 33.5; 53.5; 68.1; 101.0; 121.8; 138.4; 139.1; 140.4; 146.4; 191.8; 209.8. MS (70 eV): 234 (27, M^+), 205 (9), 145 (90), 117 (100), 115 (44), 105 (40), 91 (73), 77 (35). HR-MS: 234.1258 ($C_{14}H_{18}O_3^+$; calc. 234.1256).

*(5*R*,6*S*)-5-Acetyl-6-(2-ethoxyethenyl)-5-methylcyclohexa-1,3-diene-1-carboxaldehyde* ((5*R*,6*S*)-**11**). In a pressure-resistant *Schlenk* tube, 1.5M ^{t}BuLi in pentane (2.0 ml, 3.0 mmol) was added dropwise at −78° to a soln. of (1*Z*)-1-bromo-2-ethoxyethene (0.150 ml, 1.5 mmol) and 3-(*tert*-butyl)-4-hydroxy-5-methylphenyl sulfide (2 mg) in Et_2O (3 ml). After stirring for 1 h, a cold (−78°) soln. of complex **10** (323 mg, 1.0 mmol)

and (*S*,*S*)-**29** (484 mg, 2.0 mmol) in Et_2O (5 ml) and toluene (2 ml) was transferred *via* cannula. The soln. was stirred at $-50°$ for 20 h. After recooling to $-78°$, MeI (0.62 ml, 10.0 mmol) and HMPA (1.75 ml, 10.0 mmol) were added. The rubber septum was replaced with an adaptor fitted with a small pressure gauge. After a freeze/pump/thaw cycle, 2.5 bar CO was pressed onto the mixture. The mixture was warmed slowly to r.t. and stirred for 22 h. Excess CO was vented and volatiles were evaporated. The residue was dissolved in THF (10 ml), and 2M NaOEt in EtOH (0.75 ml, 1.5 mmol) was added at $-78°$, followed, after stirring for 15 min, by MeI (0.62 ml, 10.0 mmol). The soln. was slowly warmed to r.t. over 2 h and stirred for an additional 3 h. Volatiles were evaporated, the residue was dissolved in Et_2O and filtered through a short layer of silica gel. Purification by FC afforded (5*R*,6*S*)-**11** (97 mg, 42%). Yellow oil. GC (*Lipodex E*, 130°, H_2, 50 kPa): t_R 32.6 ((5*S*,6*R*)-**11**, minor) and 33.8 ((5*R*,6*S*)-**11**, major); ee 76%.

*[(2*R*)-*N*-(η⁶-Benzylidene)-1-methoxy-3-methylbutan-2-amine]tricarbonylchromium* (**30**). To a soln. of D-valinol (8.57 g, 0.102 mol) in dry Et_2O (180 ml) was added [Cr(benzaldehyde)$(CO)_3$] (**3**; 16.8 g, 69.0 mmol) at r.t. The mixture was stirred for 18 h and then evaporated. The residue was dissolved in dry THF (120 ml), and 55–65% NaH dispersion in oil (3.32 g) was added in small portions at r.t. After stirring for 2 h, MeI (5.17 ml, 83.1 mmol) was added, and stirring was continued overnight. The solvent was evaporated, and the residue was taken up in hexane and filtered through *Celite* under N_2. Recrystallization from hexane furnished **30** (19.10 g, 80%). Orange crystals. M.p. 56–59°. $[\alpha]_D^{20} = -157.6$ ($c = 1.5$, $CHCl_3$). IR ($CHCl_3$): 2964, 1976, 1645, 1602. ^{1}H-NMR (200 MHz, $CDCl_3$): 0.93 (*d*, *J* = 6.7, 3 H, *Me*$_2$CH); 1.03 (*d*, *J* = 6.7, 3 H, *Me*$_2$CH); 1.80–1.98 (*m*, Me$_2$C*H*); 3.00–3.12 (*m*, H–C(2)); 3.12 (*s*, MeO); 3.32–3.48 (*m*, 2 H–C(1)); 4.30–4.4 (*m*, 3 arom. H); 5.17 (*d*, *J* = 6.2, 1 arom. H); 5.42 (*d*, *J* = 5.8, 1 arom. H); 7.40 (*s*, H–C=N). ^{13}C-NMR (50 MHz, $CDCl_3$): 18.9; 20.4; 31.2; 59.1; 75.0; 76.3; 91.1; 91.3; 93.3; 93.8; 94.1; 101.2; 157.6; 233.0. MS (70 eV): 341 (1, M^+), 285 (18), 257 (91), 210 (11), 155 (100), 130 (15), 52 (80). HR-MS: 341.0721 ($C_{16}H_{19}CrNO_4^+$; calc. 341.0719). Anal. calc. for $C_{16}H_{19}CrNO_4$: C 56.16, H 5.82, N 4.08; found: C 56.14, H 5.89, N 4.09.

*(5*S*,6*R*)-5-Acetyl-6-(2-ethoxyethenyl)-5-methylcyclohexa-1,3-diene-1-carboxaldehyde* ((5*S*,6*R*)-**11**). As described for **11**, with (1*Z*)-1-bromo-2-ethoxyethene (2.1 ml, 20 mmol), 3-(*tert*-butyl)-4-hydroxy-5-methylphenyl sulfide (20 mg), Et_2O (20 ml), and 1.7M ^{t}BuLi in pentane (23.5 ml, 40 mmol); then with **30** (3.4 g, 10 mmol; instead of **10**) in THF (50 ml), MeI (6.23 ml, 100 mmol), HMPA (17.2 ml, 100 mmol), and 4 bar CO; then with THF (150 ml), 2M NaOEt in EtOH (7.5 ml, 15 mmol), and MeI (6.2 ml, 250 mmol). FC (pentane/Et_2O 3:1, 2:1) afforded (5*S*,6*R*)-**11** (1.230 g, 53%). Yellow oil. GC (*Lipodex E*, 130°, H_2, 50 kPa): t_R 32.6 ((5*S*,6*R*)-**11**, major) and 33.8 ((5*R*,6*S*)-**11**, minor); ee 95%. $[\alpha]_D^{20} = -401.9$ ($c = 1.05$, $CHCl_3$).

*(4a*S*,8a*R*)-4a,5,8,8a-Tetrahydro-4a-methyl-5-oxonaphthalene-1-carboxaldehyde* ((4a*S*,8a*R*)-**5**). To a soln. of (5*S*,6*R*)-**11** (2.720 g, 11.7 mmol) in THF (50 ml) was added 2M aq. HCl (50 ml), and the resulting mixture was refluxed at 80° overnight. After cooling to r.t., the product was extracted with Et_2O. The Et_2O layer was dried and evaporated and the residue purified by FC (silica gel, pentane/Et_2O 2:1, 1:1): (4a*S*,8a*R*)-**5** (2.23 g, 89%). Crystalline solid. GC (*Lipodex E*, 130°, H_2, 50 kPa): t_R 30.7 ((4a*S*,8a*R*)-**5**, major) and 33.8 ((4a*R*,8a*S*)-**5**, minor); ee 99%. M.p. 89–90° (hexane). $[\alpha]_D^{20} = +685.9$ ($c = 0.39$, $CHCl_3$). IR ($CHCl_3$): 3019, 2821, 1669, 1560, 1216. ^{1}H-NMR ($CDCl_3$, 400 MHz): 1.22 (*s*, Me–C(4a)); 2.19 (*ddd*, *J* = 2.5, 11.3, 17.6, 1 H–C(8)); 2.39 (*ddd*, *J* = 5.8, 5.9, 17.3, 1 H–C(8)); 3.30 (*dd*, *J* = 11.3, 4.7, H–C(8a)); 6.05 (*d*, *J* = 9.3, H–C(2)); 6.17 (*dd*, *J* = 2.5, 10.1, H–C(6)); 6.39 (*dd*, *J* = 9.3, 5.3, H–C(3)); 6.87 (*d*, *J* = 5.3, H–C(4)); 7.12 (*ddd*, *J* = 2.5, 6.2, 10.2, H–C(7)); 9.62 (*s*, CHO). ^{13}C-NMR (100 MHz, $CDCl_3$): 20.9; 26.8; 35.9; 47.4; 123.7; 129.8; 139.4; 139.6; 140.3; 151.6; 192.0; 198.9. MS: 188 (0.2, M^+), 160 (0.5), 145 (0.5), 119 (4), 91 (8), 68 (100), 65 (5). HR-MS: 188.0844 ($C_{12}H_{12}O_2^+$; calc. 188.0837). Anal. calc. for $C_{12}H_{12}O_2$ (188.08): C 76.57, H 6.43; found: C 76.57, H 6.47.

*(1*R*,4a*R*,8a*S*)-1,4,4a,8a-Tetrahydro-5-(hydroxymethyl)-8a-methylnaphthalen-1-ol* ((1*R*,4a*R*,8a*S*)-**12**). To a soln. of (4a*S*,8a*R*)-**5** (1.510 g, 8.0 mmol) and $CeCl_3 \cdot 7\,H_2O$ (8.970 g, 24.0 mmol) in MeOH (140 ml), $NaBH_4$ (0.900 g, 24.0 mmol) was added in portions at 0°. After stirring for 1.5 h, H_2O was added, the mixture extracted with AcOEt, the org. phase evaporated, and the residue purified by FC (pentane/Et_2O 1:2): (1*R*,4a*R*,8a*S*)-**12** (1.49 g, 98%). White solid. M.p. 94–96° (AcOEt). $[\alpha]_D^{20} = -57.9$ ($c = 0.33$, $CHCl_3$). IR ($CHCl_3$): 3608, 3445, 1601, 1236. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.14 (*s*, Me–C(8a)); 1.88–1.92 (*m*, H–C(4a)); 2.15–2.24 (*m*, 2 H–C(4)); 4.09–4.12 (*m*, H–C(1)); 4.16 (*d*, *J* = 4.3, CH_2–C(5)); 5.52–5.58 (*m*, *J* = 10.1, H–C(6)); 5.79–5.98 (*m*, H–C(2), H–C(3), H–C(7), H–C(8)). ^{13}C-NMR (100 MHz, $CDCl_3$): 22.2; 29.1; 39.2; 39.3; 65.4; 73.3; 117.7; 123.7; 129.6; 130.8; 131.7; 141.5. MS: 192 (0.5, M^+), 174 (7), 159 (2), 143 (4), 128 (5), 122 (4), 107 (13), 105 (100), 91 (13), 77 (13), 70 (83). HR-MS: 192.1197 ($C_{12}H_{16}O_2^+$; calc. 192.1150).

(4a*R*,8a*S*)-**5** afforded (1*S*,4a*S*,8a*R*)-**12**: $[\alpha]_D^{20} = +65.0$ ($c = 0.09$, $CHCl_3$).

*(1*RS*,4a*RS*,8a*SR*)-5-{[[(*tert*-Butyl)dimethylsilyl]oxy}methyl]-1,4,4a,8a-tetrahydro-8a-methylnaphthalen-1-ol* (**13a**). Et_3N (785 µl, 5.63 mmol) was added to a stirred soln. (0°) of **12** (0.900 g, 4.69 mmol) and DMAP (0.115 g, 0.94 mmol) in DMF (10 ml). After 10 min at 0°, (*tert*-butyl)chlorodimethylsilane (0.777 g, 5.16 mmol)

was added. The mixture was warmed to r.t., stirred for 1.5 h, diluted with Et_2O, and treated with a sat. $NaHCO_3$ soln. The org. phase was washed with H_2O and brine, dried ($MgSO_4$), and evaporated, and the crude product purified by FC (hexane/Et_2O 1:1): **13a** (1.35 g, 94%). Oil. IR ($CHCl_3$). 3619, 2953, 2856, 1463, 1360, 1252, 1158, 1126, 1067, 1022, 930, 842. ^{1}H-NMR (200 MHz, $CDCl_3$): 0.08 (*s*, Me_2Si); 0.91 (*s*, ^{t}BuSi); 1.12 (*s*, Me–C(8a)); 1.67 (br. *d*, OH); 1.72–1.95 (*m*, H–C(4a)); 2.02–2.12 (*m*, 2 H–C(4)); 4.05–4.09 (*m*, H–C(1)); 4.10–4.18 (*m*, CH_2–C(5)); 5.52–5.65 (*m*, H–C(6)); 5.73–6.00 (*m*, H–C(2), H–C(3), H–C(7), H–C(8)). ^{13}C-NMR (50 MHz, $CDCl_3$): –5.4; 18.5; 22.3; 25.9; 29.2; 39.1; 39.4; 65.4; 73.6; 116.2; 124.0; 129.5; 129.8; 131.9; 141.9. MS: 263 (8), 247 (17), 179 (59), 149 (31), 105 (100), 75 (94).

*(1*R*,4a*R*,8a*S*)-1,4,4a,8a-Tetrahydro-5-{[(4-methoxybenzyl)oxy]methyl}-8a-methylnaphthalen-1-ol* ((1*R*,4a*R*,8a*S*)-**13b**). A cold (–60°) soln. of (1*R*,4a*R*,8a*S*)-**12** (0.214 g, 1.1 mmol) in DMF (11 ml) was added to NaH (38 mg, 1.44 mmol) at –60°. After stirring for 15 min, 4-methoxybenzyl iodide (0.36 g, 1.44 mmol) was introduced in one portion, and the mixture was stirred for 3 h at –50°. After completion of the reaction (TLC monitoring), H_2O was added, and the product was extracted with Et_2O. Evaporation followed by FC (silica gel, pentane/Et_2O 1:2) furnished (1*R*,4a*R*,8a*S*)-**13** (0.310 g, 88%). Colorless oil. $[\alpha]_D^{20} = -4.0$ ($c = 0.9$, $CHCl_3$). IR ($CHCl_3$): 3444, 1610, 1248. ^{1}H-NMR ($CDCl_3$, 400 MHz): 1.17 (*s*, Me–C(8a)); 1.87–1.92 (*m*, 1 H–C(4)); 2.16–2.28 (*m*, H–C(4a), 1 H–C(4)); 3.82 (*s*, MeO); 3.95 (*d*, $J = 12.9$, 1 H, CH_2–C(5)); 4.08 (*d*, $J = 12.9$, 1 H, CH_2–C(5)): 4.10–4.12 (*m*, H–C(1)); 4.42 (*d*, $J = 11.4$, 1 H, ArCH_2); 4.50 (*d*, $J = 11.4$, 1 H, ArCH_2); 5.60 (*dd*, $J = 10.2, 1.3$, H–C(2)); 5.83–5.98 (*m*, H–C(3), H–C(6), H–C(7), H–C(8)); 6.90 (*d*, $J = 8.8$, 2 arom. H); 7.29 (*d*, $J = 8.8$, 2 arom. H). ^{13}C-NMR (100 MHz, $CDCl_3$): 22.6; 29.0; 39.4; 39.5; 55.2; 71.5; 72.2; 73.3; 113.7; 119.5; 123.7; 129.2; 129.5; 130.4; 130.9; 131.8; 139.2; 159.1. MS: 242 (2, [*M* – CH_2CH=$CHCHOH$]$^+$), 190 (1), 137 (26), 122 (17) 121 (100), 106 (48), 70 (16). HR-MS: 242.1302 ($C_{16}H_{18}O_2^+$; calc. 242.1307).

*Acetic Acid 5-{[[(*tert*-Butyl)dimethylsilyl]oxy}methyl}-1,4,4a,8a-tetrahydro-8a-methylnaphthalen-1-yl Ester* (**14a**). Ac_2O (310 µl, 3.27 mmol) was added dropwise to a soln. of **13a** (500 mg, 1.63 mmol), pyridine (0.265 ml, 3.27 mmol), and a catalytic amount of DMAP (40 mg) in CH_2Cl_2 (10 ml) at 0°. The mixture was stirred for 2 h at r.t., then diluted with CH_2Cl_2, and washed with 1N HCl, sat. aq. $NaHCO_3$ soln., and brine. The org. phase was dried ($MgSO_4$), and evaporated, and the residue purified by FC (pentane/Et_2O 4:1): **14a** (520 mg, 91%). Colorless oil. IR ($CHCl_3$): 2935, 2857, 1736, 1721, 1462, 1371, 1252, 1158, 1079, 1023, 839. ^{1}H-NMR (200 MHz, $CDCl_3$): 0.07 (*s*, Me_2Si); 0.91 (*s*, ^{t}BuSi); 1.06 (*s*, Me–C(8a)); 1.85–2.20 (*m*, H–C(4a), 2 H–C(4)); 2.13 (*s*, MeCO); 4.14 (br. *s*, CH_2–C(5)); 5.24–5.30 (*m*, H–C(2)); 5.42–5.65 (*m*, H–C(8)); 5.65–5.83 (*m*, H–C(6)); 5.95–6.00 (*m*, H–C(3), H–C(7)). ^{13}C-NMR (100 MHz, $CDCl_3$): –5.5; 18.4; 21.1; 22.0; 25.8; 29.0; 38.2; 39.1; 65.2; 75.7; 116.0; 123.9; 126.1; 129.9; 132.9; 141.8; 171.0. MS: 291 (7), 235 (8), 179 (16), 105 (97), 70 (88).

*Carbonic Acid 5-{[[(*tert*-butyl)dimethylsilyl]oxy}methyl}-1,4,4a,8a-tetrahydro-8a-methylnaphthalen-1-yl Methyl Ester* (**15a**). Methyl carbonochloridate (0.464 ml, 6.01 mmol) was added dropwise to a soln. of **13a** (1.15 g, 3.73 mmol), pyridine (1.09 ml, 13.5 mmol), and a catalytic amount of DMAP in CH_2Cl_2 (8 ml) at 0°. The mixture was stirred for 2.5 h, then diluted with CH_2Cl_2, and washed with 1N HCl, sat. aq. $NaHCO_3$ soln. and brine. The org. phase was dried ($MgSO_4$), and evaporated, and the residue purified by FC (pentane/Et_2O 9:1): **15a** (1.279 g, 94%). Colorless oil. IR ($CHCl_3$): 3041, 3008, 2953, 2943, 2856, 1741, 1708, 1442, 1365, 1268, 1158, 1077, 984, 837. ^{1}H-NMR (200 MHz, $CDCl_3$): 0.00 (*s*, Me_2Si), 0.84 (*s*, ^{t}BuSi); 1.00 (*s*, Me–C(8a)); 1.76–1.88 (*m*, H–C(4a)); 2.04–2.15 (*m*, 2 H–C(4)); 3.74 (*s*, MeO)); 5.02–5.08 (*m*, H–C(1)); 5.45–5.52 (*m*, H–C(5)); 5.66–5.70 (*m*, H–C(3)); 5.78–5.90 (*m*, H–C(2), H–C(6), H–C(7)). ^{13}C-NMR (50 MHz, $CDCl_3$,): –4.1; 18.9; 22.5; 29.7; 39.0; 39.6; 55.3; 65.8; 80.7; 116.7; 124.1; 126.1; 130.1; 133.9; 142.1; 156.6. MS: 288 (14), 235 (5), 179 (100), 157 (28), 105 (50).

*Carbonic Acid (1*S*,4a*S*,8a*R*)-1,4,4a,8a-Tetrahydro-5-{[(4-methoxybenzyl)oxy]methyl}-8a-methylnaphthalen-1-yl Methyl Ester* ((1*S*,4a*S*,8a*R*)-**15b**). Methyl carbonochloridate (0.18 ml, 2.3 mmol) was added dropwise to a soln. of (1*S*,4a*S*,8a*R*)-**13b** (451 mg, 1.44 mmol), pyridine (0.42 ml, 5.2 mmol), and a catalytic amount of DMAP in CH_2Cl_2 (3 ml) at 0°. The mixture was stirred for 15 h, then diluted with CH_2Cl_2, and washed with 1N HCl, sat. aq. $NaHCO_3$ soln., and brine. The org. phase was dried ($MgSO_4$) and evaporated, and the residue purified by FC (pentane/Et_2O 4:1): (1*S*,4a*S*,8a*R*)-**15b** (522 mg, 95%). Colorless oil. $[\alpha]_D^{20} = +61$ ($c = 0.11$, $CHCl_3$). IR ($CHCl_3$): 3015, 1741, 1664, 1612, 1274. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.15 (*s*, Me–C(8a)); 1.87–1.96 (*m*, 1 H–C(4)); 2.19–2.36 (*m*, H–C(4a), 1 H–C(4)); 3.83 (*s*, COOMe); 3.84 (*s*, MeO); 3.97 (*dd*, $J = 1.3$, 12.9, 1 H, CH_2–C(5)); 4.08 (*dd*, $J = 1.3$, 13.1, 1 H, CH_2–C(5)); 4.43 (*d*, $J = 11.4$, 1 H, ArCH_2); 4.51 (*d*, $J = 11.6$, 1 H, ArCH_2); 5.15–5.18 (*m*, H–C(1)); 5.57–5.62 (*m*, H–C(2)); 5.83–603 (*m*, H–C(3), H–C(6), H–C(7), H–C(8)); 6.90 (*d*, $J = 8.6$, 2 arom. H); 7.29 (*d*, $J = 8.6$, 2 arom. H). ^{13}C-NMR (100 MHz, $CDCl_3$): 22.2; 28.9; 38.6; 39.4; 54.7; 55.2; 71.6; 72.1; 80.0; 113.8; 119.3; 123.7; 125.5; 129.2; 130.3; 130.7; 133.3; 139.0; 156.0; 159.1. MS: 370 (0.2, M^+), 242 (7), 137 (34), 121 (100), 106 (52), 77 (7). HR-MS: 370.1738 ($C_{22}H_{26}O_5^+$; calc. 370.1781).

Pd-Catalyzed Allylic Substitution of **14a** *with [Pd(PPh$_3$)$_4$] as Catalyst.* A mixture of acetate **14a** (696 mg, 2.0 mmol) and [Pd(PPh$_3$)$_4$] (219 mg, 0.20 mmol) in NMP (8 ml) was stirred at 60° for 5 h in the presence of the sodium salt of dimethyl methylmalonate (**18**) (prepared from **18** (0.800 ml 6.00 mmol) and NaH (0.159 g, 6.00 mmol) in NMP (10 ml)). H_2O was added, the mixture extracted with Et_2O, the org. phase washed with H_2O and brine, dried ($MgSO_4$), and evaporated and the residue purified by FC (pentane/Et_2O): inseparable mixture **16a**/**17a** 7:3 (0.729 g, 84%). Colorless oil.

Partial Data of **16a**: ^{1}H-NMR (400 MHz, $CDCl_3$): 0.09 (*s*, 6 H); 0.93 (*s*, 9 H); 1.00 (*s*, 3 H); 1.31 (*s*, 3 H); 1.35–1.45 (*m*, 2 H); 1.97 (*dd*, *J* = 3.8, 10.9, 1 H); 2.94–3.03 (*m*, 1 H); 3.71 (*s*, 3 H); 3.72 (*s*, 3 H); 4.06–4.18 (*m*, 2 H); 5.32 (*d*, *J* = 9.5, 1 H); 5.44–5.48 (*m*, 1 H); 5.57 (*dd*, *J* = 2.5, 11.1, 1 H); 5.74 (*dd*, *J* = 5.3, 9.4, 1 H); 5.77–5.81 (*m*, 1 H). ^{13}C-NMR ($CDCl_3$, 100 MHz): –5.5; 16.0; 18.4; 23.7; 24.9; 25.8; 36.2; 49.3; 40.6; 52.4; 56.7; 64.6; 116.4; 119.6; 125.7; 133.1; 136.4; 139.8; 171.6; 171.8.

Partial Data of **17a**: ^{1}H-NMR (400 MHz, $CDCl_3$): 0.08 (*s*, 3 H); 0.10 (*s*, 3 H); 0.92 (*s*, 9 H); 1.04 (*s*, 3 H); 1.43 (*s*, 3 H); 1.49–1.55 (*m*, 1 H); 1.75–1.85 (*m*, 1 H); 2.05 (*dd*, *J* = 3.4, 11.2, 1 H); 3.04–3.09 (*m*, 1 H); 3.72 (*s*, 3 H); 3.74 (*s*, 3 H); 4.07–4.19 (*m*, 2 H); 5.34 (*d*, *J* = 9.1, 1 H); 5.51 (*dd*, *J* = 3.0, 10.1, 1 H); 5.60 (*dd*, *J* = 2.4, 10.1, 1 H); 5–71-5.83 (*m*, 2 H).

Pd-Catalyzed Allylic Substitution of **15a** *with [Pd(PPh$_3$)$_4$] as Catalyst.* As described above with carbonate **15a** on a 2.2-mmol scale at r.t. for 4 h: **16a**/**17a** 7:3 (865 mg, 91%).

Pd-Catalyzed Allylic Substitution of **15b** *with [Pd(PPh$_3$)$_4$] as Catalyst.* As described above (**15a** → **16a**/**17a**), with **15b** on a 0.4-mmol scale: **16b**/**17b** 75:25 (0.120 g, 67%).

Data of Pure **16b** (as obtained below from the reaction with [Pd(dppe)$_2$]). IR ($CHCl_3$): 3549, 3007, 2954, 1731, 1612, 1513, 1454, 1247, 1109, 909. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.06 (*s*, Me); 1.31 (*s*, Me); 1.31–1.42 (*m*, 2 H–C(1)); 2.13–2.17 (*m*, H–C(8a); 2.96–3.01 (*m*, H–C(2)); 3.72 (*s*, CO_2Me); 3.67 (*s*, CO_2Me); 3.82 (*s*, MeO); 3.90 (*d*, *J* = 13.4, 1 H); 4.11 (*d*, *J* = 12.6, 1 H); 4.37 (*d*, *J* = 11.4, 1 H); 4.51 (*d*, *J* = 11.4, 1 H); 5.40 (*d*, *J* = 9.6, H–C(5)); 5.49 (*dd*, *J* = 1.5, 10.1, H–C(4)); 5.58 (*dd*, *J* = 2.3, 10.1, H–C(3)); 5.75 (*dd*, *J* = 5.3, 9.4, H–C(6)); 5.85 (*d*, *J* = 5.1, H–C(7)); 6.91 (*d*, *J* = 8.6, 2 arom. H); 7.29 (*d*, *J* = 8.6, 2 arom. H). ^{13}C-NMR (100 MHz, $CDCl_3$): 16.0; 23.4; 25.3; 36.4; 39.3; 40.9; 52.4; 55.2; 56.7; 71.3; 71.8; 113.7; 119.4; 119.6; 126.0; 129.2; 130.4; 134.1; 135.9; 137.0; 159.1; 171.7; 171.8. MS: 440 (1, M^+), 158 (1), 147 (3), 122 (10), 121 (100), 77 (6). HR-MS: 440.2206 ($C_{26}H_{32}O_6^+$; calc. 440.2199).

Partial Data of **17b**: ^{1}H-NMR (400 MHz, $CDCl_3$): 1.09 (*s*, 3 H); 1.42 (*s*, 3 H); 1.57–1.67 (*m*, 1 H); 1.80–1.90 (*m*, 1 H); 2.22 (*dd*, *J* = 3.5, 10.9, 1 H); 3.03–3.10 (*m*, 1 H); 3.71 (*s*, 3 H); 3.73 (*s*, 3 H); 3.83 (*s*, 3 H); 3.90 (*d*, *J* = 12.6, 1 H); 4.11 (*d*, *J* = 12.9, 1 H); 4.41 (*d*, *J* = 11.4, 1 H); 4.50 (*d*, *J* = 11.4, 1 H); 5.41 (*d*, *J* = 9.4, 1 H); 5.50–5.62 (*m*, 2 H); 5.72–5.78 (*m*, 1 H); 5.86 (*d*, *J* = 5.1, 1 H); 6.90 (*d*, *J* = 8.4, 2 H); 7.29 (*d*, *J* = 8.4, 2 H).

Pd-Catalyzed Allylic Substitution of **15b** *with [Pd(PPh$_3$)$_4$] as Catalyst in the Absence of Base.* A mixture of **15b** (0.150 g, 0.41 mmol) and [Pd(PPh$_3$)$_4$] (47 mg, 0.04 mmol) in NMP (3 ml) was treated with **18** (0.16 ml, 1.2 mmol) at r.t. for 24 h. After completion of the reaction (TLC monitoring), H_2O was added, the mixture extracted with Et_2O, the org. phase washed with H_2O and brine, dried ($MgSO_4$), and evaporated, and the residue purified by FC (pentane/Et_2O 3:1): **16b**/**17b** 15:85 (0.108 g, 61%).

Pd-Catalyzed Allylic Substitution of **15b** *with [Pd(dppe)$_2$] as Catalyst in the Absence of Base.* A mixture of **15b** (0.150 g, 0.4 mmol) and [Pd(dppe)$_2$] (36 mg, 0.04 mmol) in NMP (4 ml) was treated with **18** (0.16 ml 1.2 mmol) at 50° for 6 h. After completion of the reaction (TLC monitoring), H_2O was added, the mixture extracted with Et_2O, the org. phase washed with H_2O and, brine, dried ($MgSO_4$), and evaporated, and the residue purified by FC (pentane/Et_2O 3:1): **16b**/**17b** 92:8 (0.130 g, 75%).

*2-{(2*S*,4a*S*,8a*R*)-1,2,4a,8a-Tetrahydro-8-[[(4-methoxybenzyl)oxy]methyl}-4a-methylnaphthalen-2-yl}-2-methylpropanedioic Acid Dimethyl Ester* ((2*S*,4a*S*,8a*R*)-**16b**). A mixture of (1*S*,4a*S*,8a*R*)-**15b** (1.00 g, 2.70 mmol) and [Pd(dppe)$_2$] (244 mg, 0.27 mmol) in NMP (8 ml) was treated with the sodium salt of **18** (prepared from **18** (1.08 ml, 8.1 mmol) and NaH (194 mg, 8.1 mmol) in NMP (8 ml)) for 24 h at r.t. After completion of the reaction, H_2O was added, the mixture extracted with Et_2O, the org. phase washed with H_2O and brine, dried ($MgSO_4$), and evaporated, and the residue purified by FC (pentane/Et_2O 3:1): (2*S*,4a*S*,8a*R*)-**16b** (1.19 g, 99%). Colorless oil. $[\alpha]_D^{20} = -113.8$ ($c = 0.305$, $CHCl_3$). The diastereoisomer **17b** was not observed under these conditions.

*2-{(2*S*,4a*R*,8a*R*)-1,2,4a,8a-Tetrahydro-8-[[(4-methoxybenzyl)oxy]methyl}-4a-methylnaphthalen-2-yl]propanoic Acid* ((2*S*,4a*R*,8a*R*)-**22**). A mixture of (2*S*,4a*S*,8a*R*)-**16b** (1.96 g, 4.45 mmol) and 6M aq. NaOH (2.2 ml, 13.3 mmol) in DMSO (16 ml) was heated at 130° for 4 h. After cooling to r.t., the mixture was diluted with H_2O and acidified with 1N HCl. The mixture was extracted with AcOEt, the org. layer washed with H_2O and brine, dried ($MgSO_4$), and evaporated, and the residue purified by FC (pentane/Et_2O 1:1): (2*S*,4a*R*,8a*R*)-**22** (1.53 g, 93%) as a 1:1 mixture of diastereoisomers. Colorless viscous liquid. $[\alpha]_D^{20} = -148.9$ ($c = 0.33$, $CHCl_3$). IR

($CHCl_3$): 3016, 1707, 1612, 1513, 1206. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.07 (*s*, 3 H); 1.13 (2*d*, *J* = 6.8, 3 H); 1.28–1.63 (*m*, 2 H); 2.09–2.18 (*m*, 1 H); 2.51–2.38 (*m*, 2 H); 3.83 (*s*, 3 H); 3.91 (*d*, *J* = 12.9); 3.92 (2*d*, *J* = 12.9, 12.4, 1 H); 4.15, 4.16 (2*d*, *J* = 12.9, 12.6, 2 H); 4.38, 4.39 (2*d*, *J* = 11.4, 2 H); 4.54 (*d*, *J* = 11.4, 1 H); 5.43 (*d*, *J* = 9.4, 1 H); 5.47–5.60 (*m*, 2 H); 5.76 (*dd*, *J* = 9.6, 5.3, 1 H); 5.87 (*d*, *J* = 5.1, 1 H); 6.91 (*d*, *J* = 8.6, 2 H); 7.30 (*d*, *J* = 8.6, 2 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 12.4; 12.9; 24.6; 25.5; 26.5; 36.5; 36.6; 37.2; 37.3; 40.9; 41.2; 43.2; 43.9; 53.3; 55.2; 71.2; 71.2; 71.5; 71.6; 113.7; 119.2; 119.3; 126.2; 127.9; 129.2; 130.4; 134.3; 135.3; 135.8; 137.1; 137.2; 159.1; 181.6; 181.7. MS: 368 (1, M^+), 158 (1), 122 (11), 121 (100), 91 (3), 77 (3). HR-MS: 368.2021 ($C_{23}H_{28}O_4^+$; calc. 368.1988).

*(3a*R*,4a*S*,8a*R*,9*S*,9a*S*)-3a,4,4a,8a,9,9a-Hexahydro-9-iodo-5-[[(4-methoxybenzyl)oxy]methyl]-3,8a-dimethylnaphtho[2,3-*b*]furan-2(3*H*)-one* ((3a*R*,4a*S*,8a*R*,9*S*,9a*S*)-**21**). Aq. $NaHCO_3$ soln. (0.95 g, 11.3 mmol, 22 ml) was added to (2*S*,4a*R*,8a*R*)-**22** (420 mg, 1.14 mmol) in CH_2Cl_2 (4 ml). I_2 (0.57 g, 2.2 mmol) and KI (1.14 g, 6.8 mmol) were added, and the mixture was stirred for 2.5 h at r.t. H_2O was added, the aq. phase extracted with Et_2O, the combined org. phase dried ($MgSO_4$), and evaporated, and the residue purified by FC (silica gel, pentane/Et_2O 1:1): (3a*R*,4a*S*,8a*R*,9*S*,9a*S*)-**21** (0.53 g, 94%) as a sticky foam. The two diastereoisomers (d.r. 1:1) were carefully separated by FC (silica gel).

Less-Polar Diastereoisomer: IR ($CHCl_3$): 1761, 1611, 1246. ^{1}H-NMR ($CDCl_3$, 400 MHz): 1.12 (*d*, *J* = 7.2, 1 Me); 1.26 (*s*, 1 Me); 1.52–1.54 (*m*, 2 H–C(4)); 2.25–2.30 (*m*, H–C(4a)); 2.72–2.76 (*m*, H–C(3a)); 2.84–2.87 (*m*, H–C(3)); 3.82 (*s*, MeO); 3.94 (*dd*, *J* = 13.4, 0.7, 1 H, CH_2–C(5)); 4.06 (*dd*, *J* = 13.3, 1.1, 1 H, CH_2–C(5)); 4.40 (*d*, *J* = 11.4, 1 H, ArCH_2); 4.50 (*d*, *J* = 11.4, 1 H, ArCH_2); 4.75 (*d*, *J* = 2.5, H–C(9a)); 4.91–4.92 (*m*, H–C(9)); 5.70–5.84 (*m*, H–C(6), H–C(7), H–C(8)); 6.89 (*d*, *J* = 8.2, 2 arom. H); 7.29 (*m*, 2 arom. H). ^{13}C-NMR ($CDCl_3$, 100 MHz): 8.9; 23.3; 30.7; 34.9; 36.5; 38.0; 41.9; 42.4; 55.2; 71.5; 71.6; 82.0; 113.8 (2 C); 120.0; 122.0; 129.3 (2 C); 130.2; 131.9; 139.3; 159.2; 178.6. MS: 494 (1, M^+), 231 (1), 122 (10), 121 (100), 105 (2), 91 (73), 77 (35). HR-MS: 494.0958 ($C_{23}H_{27}IO_4^+$; calc. 494.0954).

More-Polar Diastereoisomer: IR ($CHCl_3$): 1761, 1611, 1246. ^{1}H-NMR ($CDCl_3$, 400 MHz): 1.23 (*d*, *J* = 7.3, 1 Me); 1.26 (*s*, 1 Me); 1.74–1.80 (*m*, 2 H–C(4)); 2.29–2.33 (*m*, H–C(3a), H–C(4a)); 2.46–2.50 (*m*, H–C(3)); 3.81 (*s*, MeO); 3.9, 4.04 (2*d*, each *J* = 12.9, CH_2–C(5)); 4.38, 4.48 (2*d*, each *J* = 11.5, ArCH_2); 4.62–4.64 (*m*, H–C(9a)); 4.98 (*t*, *J* = 5.1, H–C(9)); 5.65 (*d*, *J* = 9.4, H–C(8)); 5.79 (*dd*, *J* = 9.4, 5.2, H–C(7)); 5.84 (*d*, *J* = 5.3, H–C(6)); 6.89 (*d*, *J* = 8.6, 2 arom. H); 7.26–7.31 (*m*, 2 arom. H). ^{13}C-NMR ($CDCl_3$, 100 MHz): 13.8; 27.2; 29.5; 37.9; 38.1; 38.6; 42.4; 42.9; 55.2; 71.5 (2 C); 80.7; 113.8 (2 C); 120.5; 121.8; 129.3 (2 C); 130.1; 132.3; 138.3; 159.2; 179.0. MS: 494 (1, M^+), 231 (1), 122 (10), 121 (100), 105 (2), 91 (73), 77 (35).HR-MS: 494.0958 ($C_{23}H_{27}IO_4^+$; calc. 494.0954).

*2-[(2*R*,4a*S*,8a*S*)-1,2,4a,8a-Tetrahydro-8-[[(methoxybenzyl)oxy]methyl]-4a-methylnaphthalen-2-yl]*-N,N-*dimethylpropanamide* ((2*R*,4a*S*,8a*S*)-**20**). A mixture of (1*R*,4a*R*,8a*S*)-**13b** (320 mg, 1.0 mmol) and 2,2-dimethoxy-*N*,*N*-dimethylpropan-1-amine (**19**; 1.18 g, 8.0 mmol) in xylene (10 ml) was stirred in a sealed tube at 150° for 12 h under N_2. After cooling to r.t., the mixture was evaporated and the residue purified by FC (Et_2O/pentane 2:1): diastereoisomer mixture (2*R*,4a*S*,8a*S*)-**20** (387 mg, 98%) (d.r. 1:1). Viscous oil. $[\alpha]_D^{20} = +155.0$ (*c* = 0.96, $CHCl_3$). IR ($CHCl_3$): 2921, 1627, 1507, 1245, 1076. ^{1}H-NMR ($CDCl_3$, 200 MHz): 1.03 (*s*, Me); 1.04 (*d*, *J* = 6.7, Me); 1.10 (*d*, *J* = 6.7, Me); 1.43–1.69 (*m*, 2 H–C(1)); 2.06–2.11 (*m*, H–C(8a)); 2.25–2.51 (*m*, H–C(2), MeC*H*CON); 2.93, 2.97, 2.99, 3.03 (4*s*, Me_2N); 3.81 (*s*, MeO); 3.91 (*d*, *J* = 13.1, 1 H); 4.09 and 4.14 (2*d*, *J* = 13.1, 1 H); 4.38, 4.39 (2*d*, *J* = 11.4, 1 H); 4.50, 4.52 (2*d*, *J* = 11.3, 1 H); 5.36–5.41 (*m*, H–C(3), H–C(4)); 5.45–5.55 (*m*, H–C(5)); 5.72–5.5.76 (*m*, H–C(6)); 5.85 (*d*, *J* = 5.0, H–C(7)); 6.88 (*d*, *J* = 8.6, 2 arom. H); 7.27 (*d*, *J* = 8.6, 2 arom. H). ^{13}C-NMR ($CDCl_3$, 100 MHz): 13.9; 14.4; 15.2; 25.46; 25.53; 25.7; 27.5; 29.6; 30.3; 35.6; 36.6; 37.3; 37.6; 37.7; 39.6; 40.6; 41.1; 41.3; 55.2; 71.3; 71.4; 71.7; 71.73; 113.7; 118.5; 119.1; 119.2; 119.3; 126.8; 128.8; 129.1; 129.2; 130.5; 130.51; 134.3; 134.5; 134.6; 135.2; 137.6; 175.6; 175.7. MS: 395 (2, M^+), 274 (1), 256 (2), 157 (3), 122 (12), 121 (100), 101 (10), 72 (21). HR-MS: 395.2456 ($C_{25}H_{33}NO_3^+$; calc. 395.2460).

*(3a*S*,4a*R*,8a*S*,9*R*,9a*R*)-3a,4,4a,8a,9,9a-Hexahydro-9-iodo-5-[[(4-methoxybenzyl)oxy]methyl]-3,8a-dimethylnaphtho[2,3-*b*]furan-2(3*H*)-one* ((3a*S*,4a*R*,8a*S*,9*R*,9a*R*)-**21**). To a soln. of the diastereoisomer mixture (2*R*,4a*S*,8a*S*)-**20** (80 mg, 0.20 mmol) in THF (4 ml) and H_2O (2 ml) was added I_2 (200 mg, 0.81 mmol) in one portion, and the mixture was stirred under N_2 for 3 h at r.t. (TLC monitoring). Sat. aq. $NaHSO_3$ soln. was added after completion of the reaction, the mixture extracted with Et_2O, the Et_2O layer washed with H_2O and brine, dried ($MgSO_4$), and evaporated, and the residue purified by FC (silica gel; pentane/Et_2O 2:1): (3a*S*,4a*R*,8a*S*,9*R*,9a*R*)-**21** (73 mg, 73%) as a 1:1 mixture of diastereoisomers. White foamy material. Data: see above.

*(3a*S*,4a*S*,8a*S*,9a*S*)-3a,4,4a,8a,9,9a-Hexahydro-5-[[(4-methoxybenzyl)oxy]methyl]-3,8a-dimethylnaphtho[2,3-*b*]furan-2(3*H*)-one* ((3a*S*,4a*S*,8a*S*,9a*S*)-**23**). Tributylstannane (1.04 ml, 3.57 mmol) and AIBN (cat. amount) were added to (3a*S*,4a*R*,8a*S*,9*R*,9a*R*)-**21** (0.7 g, 1.42 mmol) in dry toluene (15 ml), and the soln. was refluxed for 8 h. After completion of the reaction, H_2O was added, the mixture extracted with Et_2O, the org.

layer washed with brine, dried ($MgSO_4$) and evaporated, and the residue purified by FC (silica gel, pentane/Et_2O 1:1): (3a*S*,4a*S*,8a*S*,9a*S*)-**23** (0.48 g, 91%) as a sticky foam (d.r. 1:1). After intensive chromatographic separation, a pure sample of each diastereoisomer was obtained.

Less-Polar Diastereoisomer: $[\alpha]_D^{20} = -28.5$ ($c = 0.61$, $CHCl_3$). IR ($CHCl_3$): 2921, 2856, 1763, 1611, 1218. ^{1}H-NMR ($CDCl_3$, 200 MHz): 1.03 (*s*, 1 Me); 1.24 (*d*, *J* = 7.3, 1 Me); 1.26–1.63 (*m*, 3 H); 1.80–2.05 (*m*, 2 H): 2.19–2.29 (*m*, 2 H); 3.81 (*s*, MeO); 3.88 (*d*, *J* = 12.8, 1 H); 4.06 (*d*, *J* = 12.7, 1 H); 4.36 (*d*, *J* = 11.4, 1 H); 4.48 (*d*, *J* = 11.4, 1 H); 4.61–4.65 (*m*, 1 H–C(9)); 5.57–5.59 (*m*, 1 olef. H); 5.77–5.81 (*m*, 2 olef. H); 6.85–6.94 (*m*, 2 arom. H); 7.2–7.32 (*m*, 2 arom. H). ^{13}C-NMR ($CDCl_3$, 100 MHz): 13.9; 26.2; 26.9; 33.3; 38.1; 40.3; 40.6; 43.6; 55.2; 71.2; 71.8; 113.8 (2 C); 120.1; 121.2; 128.6; 129.3 (2 C); 130.3; 136.0; 137.7; 159.2; 180.2. MS: 368 (1, M^+), 157 (2), 143 (5),122 (15), 121 (100), 105 (2), 91 (4), 77 (4). HR-MS: 368.1949 ($C_{23}H_{28}O_4^+$; calc. 368.1988).

More-Polar Diastereoisomer: $[\alpha]_D^{20} = -47.5$ ($c = 1.5$, $CHCl_3$). IR ($CHCl_3$): 2921, 2856, 1763, 1611, 1218. ^{1}H-NMR ($CDCl_3$, 200 MHz): 1.02 (*s*, Me); 1.11 (*d*, *J* = 7.3, Me); 1.14–1.57 (*m*, 3 H); 1.85–1.89 (*m*, 1 H); 2.19–2.32 (*m*, 2 H); 2.72–2.75 (*m*, 1 H); 3.81 (*s*, MeO); 3.91 (*d*, *J* = 13.0, 1 H); 4.08 (*d*, *J* = 13.1, 1 H); 4.37 (*d*, *J* = 11.3, 1 H); 4.41–4.43 (*m*, 1 H); 4.49 (*d*, *J* = 11.3, 1 H); 5.61 (*d*, *J* = 8.7, 1 olef. H); 5.77–5.82 (*m*, 2 olef. H); 6.87–6.90 (*m*, 2 arom. H); 7.2–7.28 (*m*, 2 arom. H). ^{13}C-NMR ($CDCl_3$, 100 MHz): 9.1; 22.0; 26.4; 33.3; 38.3; 38.5; 40.2; 41.6; 55.2; 71.2; 71.8; 77.3; 113.7 (2 C); 120.1; 121.5; 129.2 (2 C); 130.3; 136.3; 138.2; 159.1; 179.3. MS: 368 (1, M^+), 157 (2), 143 (5), 122 (15), 121 (100), 105 (2), 91 (4), 77 (4). HR-MS: 368.2024 ($C_{23}H_{28}O_4^+$; calc. 368.1988).

*(4a*S*,8a*S*,9a*S*)-4a,8a,9,9a-Tetrahydro-5-{[(4-methoxybenzyl)oxy]methyl}-3,8a-dimethylnaphtho[2,3-*b*]furan-2(4*H*)-one* ((4a*S*,8a*S*,9a*S*)-**24**) *and (3a*S*,4a*S*,8a*S*,9a*S*)-3a,4,4a,8a,9,9a-Hexahydro-5-{[(4-methoxybenzyl)oxy]methyl}-8a-methyl-3-methylenenaphtho[2,3-*b*]furan-2(3*H*)-one* ((3a*S*,4a*S*,8a*S*,9a*S*)-**25**). A soln. of (3a*S*,4a*S*,8a*S*,9a*S*)-**23** (0.11 g, 0.3 mmol) in THF (3 ml) was added at $-78°$ to a freshly prepared LDA soln. (prepared from ^{i}Pr$_2$NH (0.054 ml, 0.39 mmol) and 1.6M BuLi in hexane (0.24 ml, 0.39 mmol). The resultant soln. was stirred for 1 h. A soln. of phenylselenyl chloride (= benzeneselenenyl chloride; 75 mg, 0.39 mmol) in THF (1 ml) was added, and the mixture was stirred for 2.5 h before treating with aq. NH_4Cl soln. The aq. phase was extracted with Et_2O and the combined org. phase dried ($MgSO_4$) and evaporated. The crude residue was dissolved in CH_2Cl_2 (5 ml), and pyridine (0.35 ml, 1.44 mmol) and 30% aq. soln. H_2O_2 (0.6 ml) were added at r.t. After stirring for 30 min, the mixture was diluted with Et_2O and washed with brine, the org. phase dried ($MgSO_4$) and evaporated, and the residue purified by FC (silica gel, pentane/Et_2O 1:1): (4a*S*,8a*S*,9a*S*)-**24** and (3a*S*,4a*S*,8a*S*,9a*S*)-**25** (72 mg, 66%) (3:2 ratio).

*Data of (4a*S*,8a*S*,9a*S*)-*__24__: $[\alpha]_D^{20} = +220.6$ ($c = 0.34$, $CHCl_3$). IR ($CHCl_3$): 3018, 2926, 2856, 1744, 1514, 1224, 1039. ^{1}H-NMR ($CDCl_3$, 200 MHz): 1.34 (*s*, Me); 1.50 (*t*, *J* = 12.1, 1 H–C(9)); 1.73 (*s*, Me); 2.01 (*dd*, *J* = 6.3, 12.1, 1 H); 2.56 (*dd*, *J* = 6.6, 15.2, 1 H–C(4)); 2.79 (br. *s*, H–C(4a)); 3.23 (*dd*, *J* = 2.3, 15.2, 1 H–C(4)); 3.79 (*d*, *J* = 11.9, 1 H); 3.81 (*s*, MeO); 4.06 (*d*, *J* = 12.1, 1 H); 4.33 (*d*, *J* = 11.6, 1 H); 4.48 (*d*, *J* = 11.6, 1 H); 4.75 (*dd*, *J* = 6.3, 11.6, 1 H); 5.54 (*d*, *J* = 9.6, H–C(8)); 5.83 (*dd*, *J* = 5.3, 9.6, H–C(7)); 5.91(br. *s*, H–C(6)); 6.91 (*d*, *J* = 8.4, 2 arom. H); 7.28 (*d*, *J* = 8.4, 2 arom. H). ^{13}C-NMR ($CDCl_3$, 50 MHz): 9.2; 24.5; 25.5; 36.4; 38.0; 43.2; 55.8; 71.9; 72.0; 78.2; 114.4 (2 C); 121.3; 122.4; 124.9; 130.1 (2 C); 130.4; 135.3; 137.6; 159.8; 161.1; 175.2. MS: 366 (M^+), 137 (1), 121 (100), 119 (4), 77 (3). HR-MS: 366.1845 ($C_{23}H_{26}O_4^+$; calc. 366.1831).

*Data of (3a*S*,4a*S*,8a*S*,9a*S*)-*__25__: $[\alpha]_D^{20} = -74.8$ ($c = 0.6$, $CHCl_3$). IR ($CHCl_3$): 3008, 2932, 1757, 1670, 1512, 1224, 1039. ^{1}H-NMR ($CDCl_3$, 200 MHz): 1.04 (*s*, 3 H); 1.43 (*t*, *J* = 12.1, 1 H); 1.58–1.79 (*m*, H–C(4), H–C(9)); 1.98 (*dd*, *J* = 12.9, 2.0, H–C(4a)); 2.12 (*dd*, *J* = 4.8, 15.2, 1 H); 2.80–2.95 (*m*, H–C(3a)); 3.81 (*s*, MeO); 3.90 (*d*, *J* = 13.1, 1 H); 4.06 (*d*, *J* = 13.4, 1 H); 4.35 (*d*, *J* = 11.4, 1 H); 4.48 (*d*, *J* = 11.4, 1 H); 4.52–4.54 (*m*, 1 H); 5.49 (*d*, *J* = 1.2, CH_2=C(3)); 5.57 (br. *d*, *J* = 8.8, H–C(8)); 5.75–5.81 (*m*, H–C(6), H–C(7)); 6.09 (*d*, *J* = 1.7, 1 H); 6.88 (*d*, *J* = 8.7, 2 arom. H); 7.26 (*d*, *J* = 8.6, 2 arom. H). ^{13}C-NMR ($CDCl_3$, 50 MHz): 26.8; 27.8; 33.6; 38.6; 39.6; 40.6; 55.8; 71.8; 72.4; 76.4; 114.3 (2 C); 120.7; 120.8; 121.7; 129.8 (2 C); 130.8; 136.3; 137.7; 141.7; 159.7; 180.0. MS: 366 (1, M^+), 137(1), 122 (10), 121 (100), 119 (2), 91 (3), 77 (4). HR-MS: 366.1829 ($C_{23}H_{26}O_4^+$; calc. 366.1831).

*(4a*S*,8a*S*,9a*S*)-4a,8a,9,9a-Tetrahydro-5-(hydroxymethyl)-3,8a-dimethylnaphtho[2,3-*b*]furan-2(4*H*)-one* ((4a*S*,8a*S*,9a*S*)-**26**) *and (3a*S*,4a*S*,8a*S*,9a*S*)-3a,4,4a,8a,9,9a-Hexahydro-5-(hydroxymethyl)-8a-methyl-3-methylenenaphtho[2,3-*b*]furan-2(3*H*)-one* ((3a*S*,4a*S*,8a*S*,9a*S*)-**27**). To a stirred soln. of **24**/**25** (167 mg, 0.46 mmol) in CH_2Cl_2 (12 ml) and H_2O (0.6 ml), DDQ (124 mg, 0.55 mmol) was added at r.t. (TLC (pentane/Et_2O 1:2) monitoring). After completion of the reaction (*ca.* 2.5 h), the mixture was diluted with CH_2Cl_2, the soln. washed with sat. $NaHCO_3$ soln., dried ($MgSO_4$), and evaporated, and the crude product purified by FC (pentane/Et_2O 1:2): **26**/**27** (90 mg, 80%) as an inseparable mixture (3:2 ratio). Colorless oil.

*(4a*S*,8a*S*)-4,4a,8a,9-Tetrahydro-3,8a-dimethylnaphtho[2,3-*b*]furan-5-methanol* ((4a*S*,8a*S*)-**28**). To **26**/**27** (25 mg, 0.1 mmol) in dry toluene (1 ml) at $-40°$ was added 1M DIBAL in THF (0.3 ml, 0.3 mmol). Progress of the reaction was followed by TLC, and excess DIBAL (0.3 ml, 0.3 mmol) was added until TLC showed

complete disappearance of the starting material (after *ca.* 3–4 h). AcOH (2 ml) was added, and the mixture was brought to r.t. and stirred for 30 min. Then the mixture was extracted with Et_2O, the org. layer washed with a sat. aq. $NaHCO_3$ soln., H_2O, and brine, dried ($MgSO_4$), and evaporated, and the residue subjected to chromatography (neutral alumina, pentane/Et_2O 1:2): (4a*S*,8a*S*)-**28** (17 mg, 73%). $[\alpha]_D^{20} = +58.8$ ($c = 0.24$, $CHCl_3$). IR ($CHCl_3$): 3444, 3013, 2924, 1665, 1456, 1227, 1102, 1017, 992. ^{1}H-NMR ($CDCl_3$, 400 MHz): 1.15 (*s*, Me); 1.54–1.78 (br. *s*, OH); 1.90 (*d*, $J = 1.1$, 3 H); 2.18–2.28 (*m*, 2 H–C(4)); 2.50 (*d*, $J = 16.7$, 1 H–C(9)); 2.54–2.58 (*m*, H–C(4a)); 2.60 (*d*, $J = 16.6$, 1 H–C(9)); 4.22 (*s*, 2 H); 5.56 (*d*, $J = 8.9$, H–C(8)); 5.88–5.93 (*m*, H–C(6), H–C(7)); 7.01 (*s*, H–C(2)). ^{13}C-NMR ($CDCl_3$, 100 MHz): 8.0; 23.7; 25.7; 35.0; 35.7; 40.1; 65.4; 118.1; 118.8; 119.0; 123.4; 136.5; 137.5; 142.7; 149.5. MS: 230 (M^+), 205 (2), 149 (6), 121 (2), 108 (100), 79 (8), 77 (4), 51 (1). HR-MS: 230.1306 ($C_{15}H_{18}O_2^+$; calc. 230.1295).

*(+)-(4a*S*,8a*S*)-15-Acetoxytubipofuran* (= *(+)-(4a*S*,8a*S*)-4,4a,8a,9-Tetrahydro-3,8a-dimethylnaphtho[2,3-*b*]-furan-5-methanol Acetate*; (+)-(*S*,*S*)-**2**). To a soln. of (4a*S*,8a*S*)-**28** (20 mg, 0.08 mmol), pyridine (0.03 ml, 0.35 mmol), and a catalytic amount of DMAP in dry CH_2Cl_2 (1.5 ml) at 0° was added Ac_2O (0.02 ml, 1.74 mmol). After stirring for 30 min, the mixture was diluted with Et_2O, the soln. washed with 5% HCl soln., sat. aq. $NaHCO_3$ soln., H_2O, and brine, dried ($MgSO_4$), and evaporated, and the residue subjected to FC (neutral alumina, pentane/Et_2O 4:1): (+)-(*S*,*S*)-**2** (22 mg, 93%). Light yellow oil which turned brown (dec.) after a few days at r.t. $[\alpha]_D^{20} = +100.3$ ($c = 0.29$, $CHCl_3$). IR ($CHCl_3$): 3019, 2921, 1730, 1649, 1572, 1376, 1218, 1022. ^{1}H-NMR ($CDCl_3$, 400 MHz): 1.14 (*s*, 1 Me); 1.91(*s*, 1 Me); 2.1 (*s*, 1 Me); 2.14–2.24 (*m*, 2 H–C(4)); 2.53 (*d*, $J = 16.4$, 1 H–C(9)); 2.54–2.61(*m*, H–C(4a)); 2.66 (*d*, $J = 16.7$, 1 H–C(9)); 4.63 (*d*, $J = 13.2$, 1 H, CH_2–C(5)); 4.70 (*d*, $J = 13.5$, 1 H, CH_2–C(5)); 5.58 (*d*, $J = 8.6$, H–C(8)); 5.88–5.91 (*m*, H–C(6), H–C(7)); 7.01 (*s*, H–C(2)). ^{13}C-NMR ($CDCl_3$, 100 MHz): 8.1; 20.8; 23.7; 25.7; 35.1; 35.8; 40.2; 66.3; 118.9; 119.0; 120.9; 123.3; 136.5; 137.7; 138.2; 149.4; 170.8. MS: 272 (M^+), 205 (2), 165 (0.5), 149 (4), 123 (1), 108 (100), 79 (7), 77 (6), 51 (2). HR-MS: 272.1404 ($C_{17}H_{20}O_3^+$; calc. 272.1412).

(−)-(*R*,*R*)-**2** was obtained analogously from (3a*R*,4a*S*,8a*R*,9*S*,9a*S*)-**21**. $[\alpha]_D^{20} = -120$ ($c = 0.64$, $CHCl_3$) [9]: $[\alpha]_D^{20} = +10.7$ ($c = 0.5$, $CHCl_3$)). CD: λ_{max} 274 nm (($\Delta\varepsilon - 3$) ([9]: λ_{max} 274 ($\Delta\varepsilon + 3$)).

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