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Towards EPC-syntheses of the structural class of cochleamycins and macquarimicins. Part 3: EPC-syntheses of the β-keto lactone subunits and first attempts towards the syntheses of the pentacyclic antibiotics of this group

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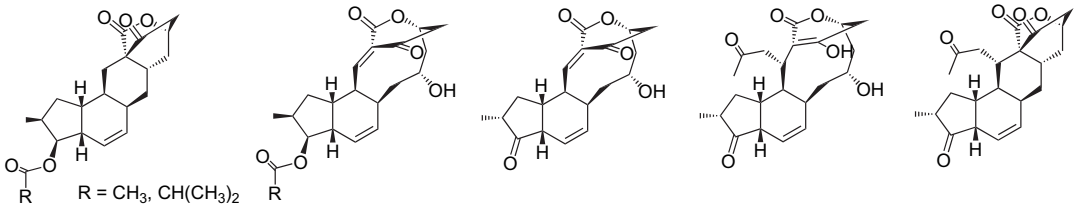
Abstract—Practical EPC-syntheses of δ-substituted-β-keto δ-lactones, subunits of the cochleamycins and macquarimicins, are presented. In consequence Tietze's tandem reaction is employed to combine δ-allyl-β-keto δ-lactone with a hydrindene derivative, the second subunit of these acetogenic antibiotics. Model reactions for the final oxidative radical tandem cyclization reveal that the electrophilic radical cyclizes exclusively in *exo-trig* fashion. However, with the intended precursor of macquarimicin C allylic hydrogen abstraction thwarted the oxidative radical tandem cyclization.

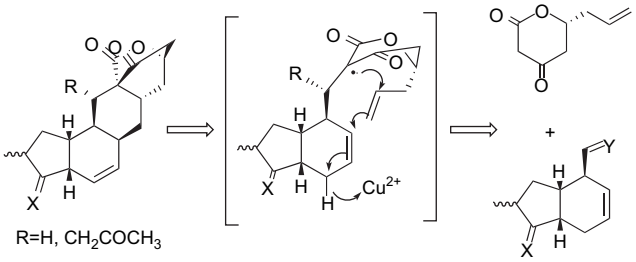
1. Introduction

Cochleamycins[1] and macquarimicins[2] (Scheme 1) are structurally related bacterial metabolites with a unique set of biological activities against bacteria, tumours, and inflammation.[3] These broad physiological activities and their intriguing new structures prompted several scientists including our group to synthesize these potential therapeutics.[4]



Scheme 1.

In the preceding publications, we described the syntheses of the hydrindene subunits of these acetogenic macrolide antibiotics.[4d] Here, we present practical EPC-syntheses of the β-keto δ-lactone subunits and our first attempts towards the syntheses of the pentacyclic antibiotics of this group.[5] To gain optimal convergence, we aimed at combining the two subunits at a very advanced stage of the synthesis. This, we hoped to achieve by connecting the β-keto lactone via substitution or Knoevenagel condensation with the exocyclic carbon atom of the hydrindene subunit followed by oxidative radical tandem cyclization as one of the last steps of the intended syntheses (Scheme 2).



Scheme 2.

Keywords: Macquarimicin; EPC-syntheses of δ-substituted-β-keto δ-lactones; Tandem Knoevenagel/hetero-Diels–Alder reaction; Regiochemistry of oxidative radical cyclization; Allyl oxidation.
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2. EPC-syntheses of the substituted β-keto δ-lactones

2.1. Synthesis of the δ-allyl-β-keto δ-lactone

Our first synthetic efforts towards this compound followed the strategy of Johnson,[6] due to the high enantioselectivity that was demonstrated and the inexpensive starting materials that were required (Scheme 3).

Commercially available 1,1-diethoxybut-3-ene[7] was transacetalized in high diastereoselectivity (20:1) to (2*S*,4*R*)-2-allyl-4-methyl-1,3-dioxane **1** with (3*R*)-butan-1,3-diol, obtained by reduction of polyhydroxybutyric acid,[8] and anhydrous $CuSO_4$ as mild catalyst. Mukaiyama aldol[9] reaction of this cyclic acetal with 1,3-bis(trimethylsiloxy)-1-ethoxybutadiene[10,11] as enolic partner and $TiCl_4$ as Lewis acid led to the 3-ketooct-7-enoic acid derivative **2** accompanied by dimerization[11] of the bis(silyl enol ether).[10] To remove the now obsolete chiral auxiliary, the primary alcohol was oxidized to the aldehyde with Dess–Martin periodinane,[12] followed by $E1_{cB}$ elimination to β-keto ester **3**. Ring closure to the desired lactone **4** was achieved by saponification and acidic lactonization.[13] To measure the enantiomeric excess by lanthanide-induced shift (LIS)[14] the methyl enol ether was produced. Treatment of lactone **4** with diazomethane yielded the enol ether **5** along with considerable amounts of the lactone methyl enolate **6**, whereas use of dimethyl sulfate under basic conditions led exclusively to enol ether **5** in >70% yield. The structure of the enol ether and the enol ester were determined by comparison with the ^{1}H NMR data of analogous compounds.[15] With enol ether **5** and commercially available Eu(hfc)$_3$ as the chiral-shift reagent, LIS revealed excellent enantiomeric excess (>95% ee). However, yields by Johnson's method were not satisfactory and workup was laborious. Therefore, we opted for a chiron approach. Commercially available (*S*)-ethyl 4-chloro-3-hydroxybutanoate was converted to the unsaturated hydroxy ester **7**, according to the literature, within four steps.[16] Claisen condensation of the lithium enolate of *tert*-butyl acetate and (*R*)-**7** at low temperature afforded the β-keto ester (*R*)-**8** in 78% yield.[17] Final lactonization with trifluoroacetic acid furnished (*R*)-**4** in high yield (Scheme 4).

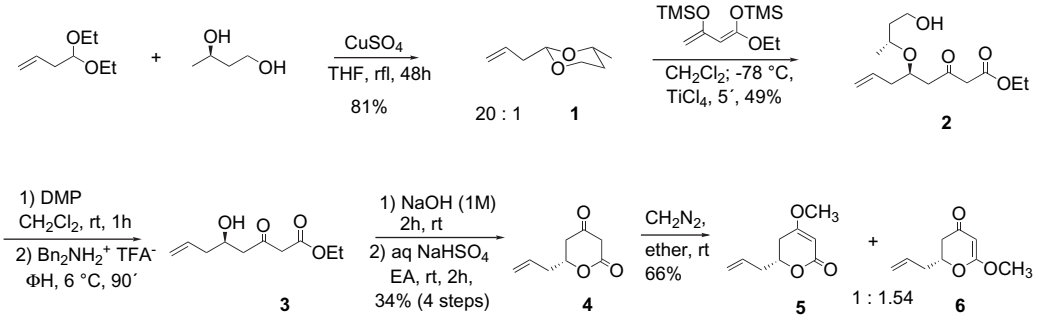
2.2. Preparation of the orthogonally protected β-keto lactone 16

Preparation of **16**, which is necessary for the tetracyclic antibiotics (cochleamycins A and macquarimicins A and B) was achieved by choosing Nagao's aldol condensation as the key step.[18]

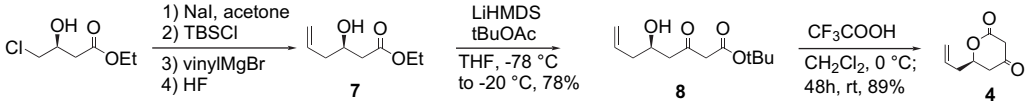
The known aldehyde **11**,[19] which we obtained starting with (*S*)-malic acid and proceeding in analogy to the protocol of Paterson et al.,[20] was reacted with (*R*)-*N*-acetylthiazolidinethione[21] catalyzed with rigorously dried tin(II) triflate. The desired C-2 chain extended *N*-acylthiazolidinethione **12** was prepared in 81% yield and with very good diastereoselectivity (16.5:1). Easy separation on silica gel was followed by removal of the chiral auxiliary with ethanol and DMAP. The relative configuration of the two stereogenic centres in the newly formed substituted hexanoic ester **14** was ascertained by acetalization via DDQ oxidation,[22] which led in the case of the major product **14** to a single cyclic acetal **17**. NOESY spectra revealed that all substituents of this 1,3-dioxane derivative were equatorially positioned, thus confirming that the desired *cis*-1,3-diol had been formed. Further chain extension via Claisen condensation with the lithium salt of *tert*-butyl acetate and acidic cyclization of the generated *tert*-butyl octanoate derivative **15** with trifluoroacetic acid completed the synthesis to the β-keto lactone **16** (Scheme 5). Having succeeded in the enantiomerically pure preparation of subunits of our planned syntheses, we turned to the most challenging task, the combination of the subunits.

2.3. Attempts to combine the hydrindenes with the lactone subunits

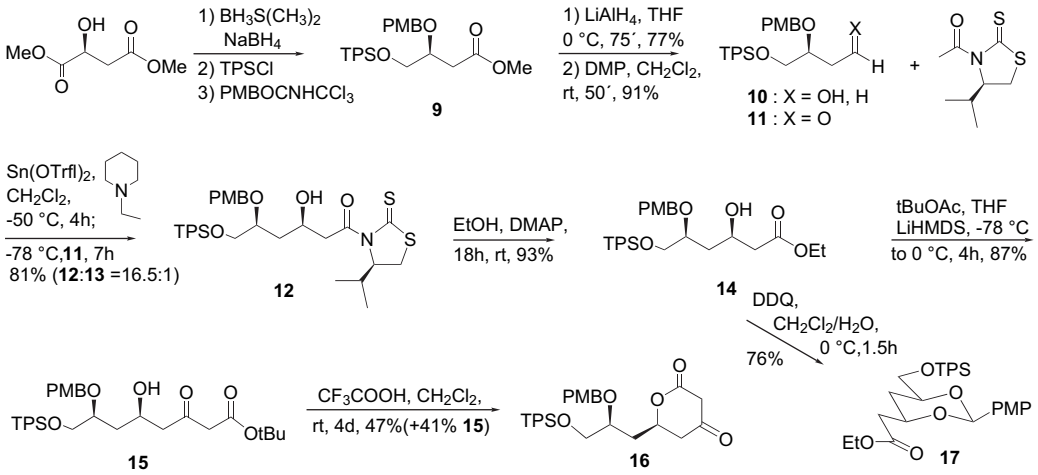
As mentioned above it was our intention to link the subunits at a very late stage in the synthesis by using nucleophilic substitution or Knoevenagel condensation.[23] Nucleophilic substitution seemed preferable due to the instability of β,γ-unsaturated aldehydes and the high reactivity of the Knoevenagel adduct. Our first attempt to get the coupled product by substitution was to use the Mitsunobu reaction.



Scheme 3.



Scheme 4.



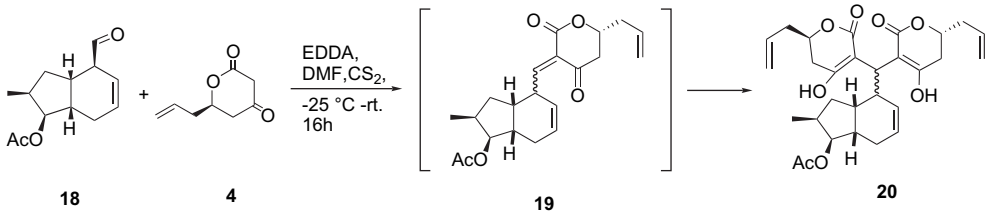
Scheme 5.

However, conditions described in the literature did not lead to the desired product.[24] Having failed with this protocol, we examined substitution of the β-keto lactone with model iodides and tosylates, but this was also unsuccessful.[25] Thus Knoevenagel condensation had to be examined. β-Keto esters and especially β-keto lactones easily react with aldehydes to give the expected adducts, but their high reactivity leads to immediate addition of a second β-dicarbonyl unit via Michael reaction.[23,26] Under acidic conditions even a second aldehyde moiety reacts with such Knoevenagel adducts.[27] Further obstacles are their general instability[27,28] and the ease of tautomerization of Knoevenagel adducts with enolizable aldehydes.[27,29] We reasoned that the steric hindrance of aldehydes **18** and **21** might prevent these consecutive reactions and the very mild conditions necessary for these Knoevenagel reactions might be compatible with the unstable unsaturated aldehyde as well as with the labile Knoevenagel adduct.[30] As it turned out, the assumption that steric hindrance would prevent the consecutive Michael reaction was incorrect. Hydrindene aldehyde **18**, the subunit of the cochleamycin B synthesis, and β-keto lactone **4** were treated in a mixture of CS_2 and DMF as solvent with ethylendiammonium diacetate (EDDA) at −40 to −30 °C (Scheme 6).

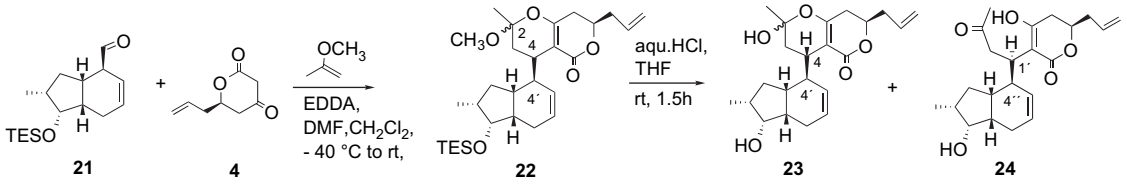
The main compound isolated was the product **20**, formed by the Knoevenagel condensation to give **19**, followed by Michael addition of a second β-keto lactone unit. Our attempts to prevent this consecutive reaction by in situ reduction and/or addition of the reductant at low temperatures after short reaction times failed.[31] Addition of benzenethiol, as described by Paquette,[32] was unsuccessful too. Tietze has demonstrated that these reactive adducts are very good heterodienes for electron-rich dienophiles, which add faster than either aldehydes or β-dicarbonyl compounds to the Knoevenagel adducts.[33] In the case of cochleamycin B, we had to look for dienophiles that could be removed after isolation of the Diels–Alder adduct. The most likely candidates as dienophiles seemed to us to be unsaturated sulfur compounds. Attempts to use liquid sulfur dioxide as solvent and addend failed.[34] Although the starting aldehyde disappeared, it reappeared by working up the reaction mixture. Obviously aldehyde adduct formation with SO_2 is faster than the Knoevenagel reaction. Several examples of hetero-Diels–Alder reactions with thiono compounds under rather mild conditions are known in the literature,[35] but none of the thiono compounds examined (carbon disulfide, dimethyl trithiocarbonate, tetramethylthiourea, thiobenzophenone, phenyl isothiocyanate) added faster to adduct **19** than a further β-keto lactone moiety.

Thus we turned to aldehyde **21**, the subunit of the planned synthesis of the macquarimicins, where Tietze's tandem reaction not only would prevent the consecutive Michael addition with the β-keto lactone but also would allow the introduction of the necessary side chain. Aldehyde **21** and β-keto lactone **4** were stirred in excess 2-methoxypropene, THF and EDDA (Scheme 7).[33]

Indeed, the enol ether added faster than a second β-keto lactone to the elusive Knoevenagel product, indicated by signals in the ^1H NMR spectrum of the crude reaction mixture. Singlets in the range of signals of methoxy groups (3.39 and 3.02 ppm) and methyl groups (1.13 and 1.46 ppm) were in accordance with the substituents at the anomeric centre of the desired adduct(s) **22**. Analyses of the spectra of this mixture and the spectra of products of subsequent



Scheme 6.

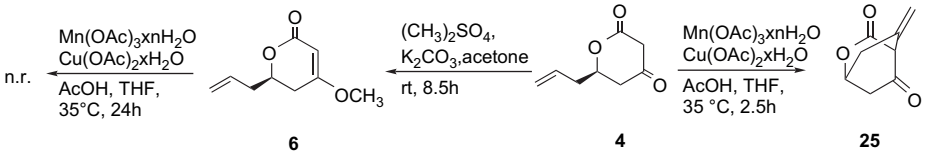


Scheme 7.

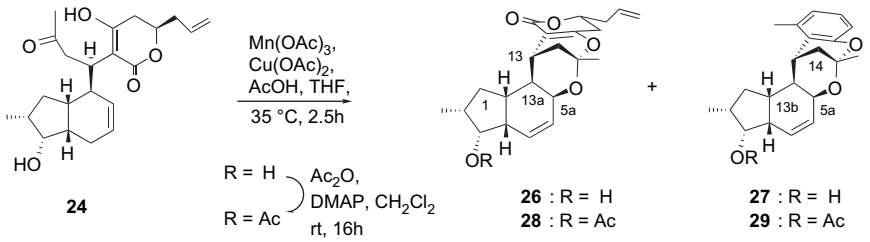
reactions revealed that a 1.15:1 ratio of two epimers of **22**, differing in configuration at C(4), were the main products, with none or only very small amounts of the corresponding anomers. We assumed, according to crosspeaks of NOESY spectra, that the energetically less favoured β-anomers had been formed. Attempts to purify the mixture on silica gel led to rather severe loss of material and incomplete separation. After chromatography, the respective anomeric products could be detected as byproducts. The insignificant selectivity, which is contrary to examples of that tandem reaction described in the literature,[36,5] prompted us to examine List's protocol using proline catalyzed Michael reaction of acetone instead of the hetero-Diels–Alder as consecutive reaction.[37] Unfortunately no trace of the desired compound **23** could be detected. Therefore, the crude reaction mixture of the Tietze reaction containing **22** was hydrolyzed immediately under weakly acidic conditions thus preventing loss of material by chromatography and reducing the number of possible diastereomers. Using 3.5% aq HCl/THF at room temperature for 1.5 h, one of the main products and its anomeric byproduct were converted to a mixture of the hemiketals **23**. Prolonged reaction time led to hydrolysis of the second main product and its anomer to a single ketone **24**.

Our next planned step as demonstrated retrosynthetically (Scheme 2) was radical tandem cyclization.[38] However, the regiochemistry of the oxidative radical cyclization[39] had to be tested. It was known that electrophilic and/or stabilized radicals tend to *endo-trig* addition.[40] In the case of 6-*exo*- versus 7-*endo-trig* cyclization, Snider et al. found with β-dicarbonyl radicals with terminal double bonds mainly *endo-trig* cyclization.[41] α-Substituted β-dicarbonyl compounds as well as 1,2-disubstituted double bonds shift the ratio of *exo* versus *endo* towards 6-*exo-trig* cyclization.[42] Thus, lactone **4** itself seemed a very suitable model to test the usefulness of this cyclization for our purpose (Scheme 8).

Treating lactone **4** in degassed acetic acid with commercially available $Mn(OAc)_3 \cdot 7H_2O$ and $Cu(OAc)_2 \cdot H_2O$ at elevated temperatures (80–90 °C)[43] led to a single product **25**, which in rapid succession aromatized. Keeping the temperature between room temperature and 35 °C permitted clean production of the bicyclic lactone **25** without double-bond isomerization and decarboxylation (no contamination >3% was observed in ^1H NMR spectra). Using ultrasound accelerated the reaction only slightly.[44] Consecutive aromatization seemed to be the reason of severe losses by chromatographic purification too. Slow aromatization to 6-methylsalicylic acid was even observed over prolonged standing of **25** at room temperature. No traces of *endo-trig* cyclization to the seven-membered ring could be detected. As an alternative, we examined the Lewis acid activated iodination.[45] None of the different protocols of iodine initiated cyclization could be successfully applied. As a further extension, we tested the possibility of cyclizing the enol ether **6** by oxidative radical reaction. No reaction occurred under similar reaction conditions as those used with β-keto lactone **4**, even at 10-fold prolonged reaction times. These results prompted us to continue our synthetic efforts with ketone **24**, although we were unable to determine with certainty the configurations at C(1′) and C(4″) of **24** at this time. Ketone **24** promised faster reaction/milder reaction conditions than the enol ether hemiketals **23**. In addition, since ketone **24** existed as essentially a single compound with only very small amounts of the corresponding hemiketals formed in solution, it was anticipated that interpretation of the results of subsequent reactions would be less difficult. Reaction conditions identical with those used with model compound **4** produced two main products, **26** and **27**, which were easily separated by chromatography (Scheme 9). Even perfunctory examination of their spectral data revealed that the desired tandem reaction (see Scheme 2) had not occurred. An additional oxygen function in an allylic position of the hydrindene part of both products and an intact allylic side chain in **26** and an aromatic subunit in **27** were most conspicuous. Compounds **26** and **27** were more stable than their precursor molecules, thus permitting extensive NMR-spectroscopic investigations, especially NOE measurements of these compounds and their corresponding acetates **28** and **29**, which in turn led to structural determination not only of these compounds but also of compounds **22**, **23** and **24**. Esterification of **26** and **27** established that the hydroxy group of the hydrindene subunit of **24** was not involved in the introduction of the newly formed allylic oxygen function despite the ease with which *cis*-hydrindenols tend to form oxygen bridges.[4d,e] Coupling constants, COSY crosspeaks, HMBC long-range correlations and NOESY crosspeaks in



Scheme 8.

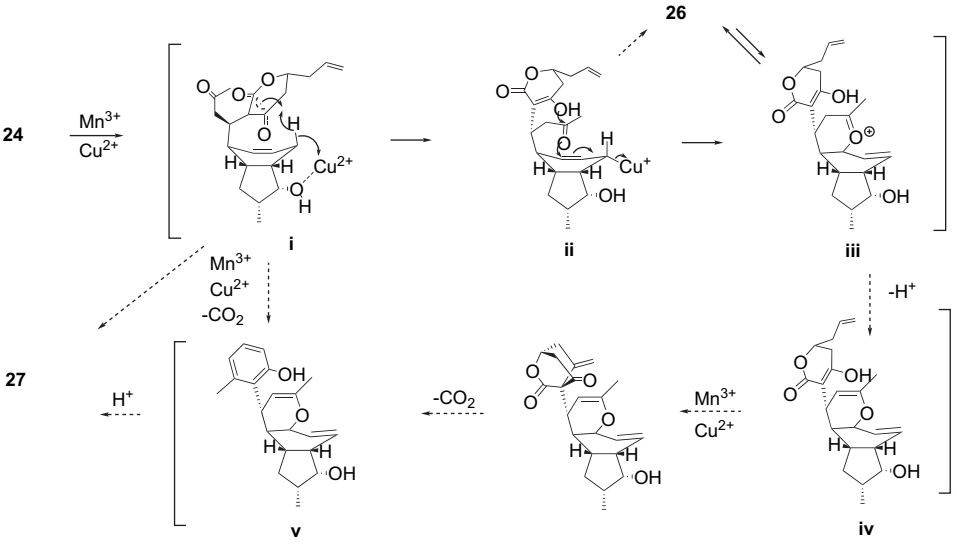


Scheme 9.

acetate **28** indicated that the newly introduced oxygen function is at position C(5a). The strong NOE between protons H(5a) and H(13a) established their vicinal cis position, whereas NOEs of H(13a)/H(1*endo*) and H(13a)/CH_3COO revealed that proton H(13a) is still in an *endo* position, confirming that no epimerization at C(13a) occurred within the Knoevenagel reaction to an observable extend. A small but significant long-range coupling (*w*-coupling) in the ^1H NMR spectrum of H(13a) and H(14*endo*) as well as a strong NOESY crosspeak H(14*exo*)/H(13b) established the *R*-configuration at C(13). Similar effects were found for the spectra of compounds **27** and **29**.

Of the several possible mechanisms, the following seems to cover most of the facts observed so far (Scheme 10). Mn(III) generates the delocalized radical at the β-keto lactone moiety (**i**). This highly congested structure with the unsaturated cyclohexene in the boat conformation promotes abstraction of the flagpole hydrogen. The generated allylic radical combines with Cu(II) (possibly directed by the hydroxy group at C(1″) yielding the organocopper species (**ii**). $S_{N'}$ reaction with an oxygen function (either the preformed hemiketal or the ketone and subsequent addition of the enol to the generated oxocarbenium) leads to **26**. Several reaction sequences to **27** are conceivable. Delocalized radical (**i**) in a reaction analogous to the sequence in Scheme 8 could attack the allylic side chain followed by double-bond isomerization, decarboxylation and aromatization. The phenol (**v**) generated could, by renewed single-electron oxidation to the delocalized phenoxyl radical, abstract the flagpole hydrogen of the hydrindene and subsequently proceed analogous from **24** to **26**. Whether the half-life of the organocopper species (**ii**) in this acidic and polar solvent is compatible with consecutive reactions is questionable. More likely the tetrahydropyrylium derivative (**iii**) in a concurring reaction is transformed to the more stable dihydropyran (**iv**) followed by renewed attack of Mn(III) at the β-keto lactone. Now attack of the allylic side chain according to Scheme 8 and isomerization of the exocyclic double bond is followed by aromatization. If this aromatization is, in analogy to the model, a polar reaction sequence or due to a retro hetero-Diels–Alder reaction[46] remains to be examined.

As mentioned above, the spectral data of its consecutive products **26**–**29** disclosed that **24** has *R*-configuration at the newly formed stereocentre C(1′), whereas the macquarimicins exhibit *S* configuration at this stereocentre. Thus, the inseparable mixture of anomers **23** would have been the possible precursor for the tandem cyclization. Indeed, upon closer examination of the NMR spectra of the main component of **23**, as expected, the α-anomer shows crosspeaks in the NOESY spectrum between H(4′) and H(3′*endo*) as well as between H(3′*endo*) and CH_3(2′), establishing the *endo* position of H(4′). Crosspeaks between H(5′) and H(3) and H(4) as well as the large coupling constant of H(4) with H(3) are in accordance with *S* configuration at C(4). Most of the signals of the minor compound are very similar to the main compound and thus concealed. The



Scheme 10.

few visible signals although nearly identical in their pattern with the analogous signals of the main compound disclose different NOEs. The very large NOE between CH_3(2) and H(4), which is conspicuously missing in the main compound, establishes the minor compound as the β-anomer.

The surprisingly fast aromatization that we observed in the reaction sequence pictured in Scheme 8 and especially Scheme 9 and the fact that enol ethers do not react under mild conditions do not bear up well with the projected radical tandem reaction with Mn(III) for **23**, where only very small amounts of the open-chain ketone can be expected in solution. More promising prospects are tandem cyclization via seleno β-keto lactone according to Ley et al.[47] or Pd(II) tandem cyclization.[48]

3. Conclusion

Practical EPC-syntheses of δ-allyl-β-keto δ-lactone **4** and orthogonally protected δ-(2,3-dihydroxypropyl)-β-keto δ-lactone **16** were achieved. Syntheses of cochleamycins and macquarimicins were attempted via substitution as well as via Knoevenagel condensation with the respective hydrindene derivatives. We succeeded when using Tietze's tandem reaction (Knoevenagel/hetero-Diels–Alder). The regiochemistry of the intended final oxidative radical tandem cyclization was examined with **4** as model. The stabilized, electrophilic radical generated with Mn(III) cyclized as desired exclusively in *exo-trig* fashion contrary to examples in the literature. In the case of intermediate **22**, identical reaction conditions led to allylic hydrogen abstraction in the hydrindene subunit and in consequence to two new pentacyclic structures **26** and **27**.

4. Experimental section

4.1. General

^{1}H and ^{13}C NMR spectra were recorded at 300 K on Avance spectrometers (Bruker Biospin GmbH, Rheinstetten, Germany), either on a DRX 400 WB or a DRX 600, with resonance frequencies of 400.13 MHz for ^{1}H and 100.61 MHz for ^{13}C, or 600.13 MHz for ^{1}H and 150.90 MHz for ^{13}C, respectively. The assignment was accomplished by 2D NMR experiments, i.e., double quantum filtered correlated spectroscopy (DQF-COSY), nuclear Overhauser effect spectroscopy (NOESY), heteronuclear single quantum correlation (HSQC) and heteronuclear multiple bond correlation (HMBC). Chemical shifts are referenced internally to the residual, non-deuterated solvent signal for ^{1}H ($CDCl_3$: δ=7.26 ppm, C_6D_6: δ=7.16 ppm) or to the carbon signal of the solvent for ^{13}C ($CDCl_3$: δ=77.00 ppm, C_6D_6: δ=128.06 ppm). The analyses of the ^{1}H–^{1}H coupling constants (given in hertz) were supported by the program SpinWorks (provided by Kirk Marat, University of Manitoba, Canada). Optical rotations were measured on a Perkin–Elmer 241 polarimeter with the Na D line. IR spectra were recorded on a Perkin–Elmer 1600 FTIR spectrometer and given in wave numbers (cm^{-1}). Melting points were obtained using a Reichert 'Kofler' hot stage microscope and are uncorrected. EI mass spectra were recorded on a Finnigan 8230 spectrometer. Unless otherwise stated, starting materials were purchased from commercial suppliers and used without further purification. Dry dichloromethane was distilled from P_2O_5 and kept over 4 Å molecular sieves. Dry THF was distilled under argon from Na/benzophenone prior to use. Silica gel (230–400 mesh ASTM, Merck) was used for flash chromatography.

4.2. (2*S*,4*R*)-2-Allyl-4-methyl-1,3-dioxane (1)

1,1-Diethoxybut-3-ene (2.88 g, 3.4 mL, 20 mmol), (*R*)-butane-1,3-diol (2.0 g, 2.0 mL, 22 mmol) and dry $CuSO_4$ (~10 mg) were refluxed under argon for 4 h. Diethyl ether was added to the cooled reaction mixture, which was then filtered through Celite and washed with diethyl ether. The solvent was removed under reduced pressure and the resulting mixture was fractionally distilled (77–80 °C, 46 mm) yielding **1** as a colourless oil (2.3 g, 16.4 mmol, 81%). A small part was further purified by flash chromatography on silica gel (pentane/diethyl ether 20:1). $[\alpha]_D^{20}$ −7.76 (*c* 1.07, $CHCl_3$). IR (cm^{-1}, film): 3078, 2974, 2948, 2922, 2852, 1644, 1464; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.22 (d, 3H, CH_3(4), $J_{CH_{3,4}}$ = 6.2), 1.41 (dddd, 1H, H(5eq), $J_{5e,5a}$=13.3, $J_{5e,4}$~$J_{5e,6e}$~2.4, $J_{5e,6a}$~2.2), 1.65 (dddd, 1H, H(5ax), $J_{5a,5e}$~13.3, $J_{5a,4}$~12.8, $J_{5a,6a}$~11.3, $J_{5a,6e}$~5.1), 2.37 (dddd, 2H, H(1′), $J_{1',2'}$=6.8, $J_{1',2}$=5.4, $J_{1',3'trans}$~$J_{1',3'cis}$~1.3), 3.71 (ddd, 1H, H(6ax), $J_{6a,6e}$=11.4, $J_{6a,5a}$~11.9, $J_{6a,5e}$=2.5), 3.73 (ddq, 1H, H(4), $J_{4,5a}$=11.2, $J_{4,5e}$=2.4, J_{4,CH_3} = 6.2), 4.08 (ddd, 1H, H(6eq), $J_{6e,6a}$=11.4, $J_{6e,5a}$=5.0, $J_{6e,5e}$~1), 4.56 (t, 1H, H(2), $J_{2,1'}$=5.3), 5.07–5.11 (m, 2H, H(3′)), 5.83 (ddt, 1H, H(2′), $J_{2',3'}$=17.2, $J_{2',3'cis}$=10.2, $J_{2',1'}$=7.0); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.7, 32.9, 39.8, 66.6, 72.8, 101.2, 117.4, 132.9; MS (EI, 70 eV, 30 °C): *m*/*z* (%)=141.2 (16.4, M^+−H), 102 (15.5), 101 (81), 71 (22), 70 (27), 69 (32), 56 (23), 55 (92), 45 (52.5), 43 (100).

4.3. (5*R*,7*R*)-Ethyl 5-allyl-9-hydroxy-7-methyl-3-oxo-6-oxanonanoate (2)

To a solution of acetal **1** (1.29 g, 9.05 mmol) and 1-ethoxy-1,3-bis(trimethylsiloxy)butadiene (15 g, 55.1 mmol) in dry dichloromethane (190 mL), $TiCl_4$ (4 mL, 36.7 mmol) was dropped with stirring under argon at −78 °C. After 5 min, the reaction was quenched with methanol. The organic layer was extracted with aq 1 N HCl (2×100 mL), then washed with water (100 mL), aq satd $NaHCO_3$ and brine, and dried (Na_2SO_4). After removal of the solvent under reduced pressure the orange-red oil was purified by flash chromatography on silica gel (dichloromethane/methanol 200:1) giving dimeric acetoacetate and **2** as orange viscous oil (1.21 g, 4.44 mmol, 49%). $[\alpha]_D^{20}$ −85.12 (*c* 1.02, $CHCl_3$). IR (cm^{-1}, film): 3436, 3077, 2972, 2934, 1745, 1714, 1641, 1445; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.11 (d, 3H, CH_3(7), $J_{CH_{3,7}}$ = 6.0), 1.25 (t, 3H, CH_3, J_{CH_{3},CH_2} = 7.2), 1.66 (dt, 2H, H(8), $J_{8,7}$~$J_{8,9}$~5.6–5.8), 2.27 (dddt, 1H, H(1′α), $J_{1'\alpha,1'\beta}$=14.1, $J_{1'\alpha,2'}$~7.2, $J_{1'\alpha,5}$=6.8, $J_{1'\alpha,3'}$~1.3), 2.33 (dddt, 1H, H(1′β), $J_{1'\beta,1'\alpha}$=14.1, $J_{1'\beta,2'}$~7.2, $J_{1'\beta,5}$=5.0, $J_{1'\alpha,3'}$~1.3), 2.42 (t, 1H, OH, $J_{OH,9}$~5.0), 2.58 (dd, 1H, H(4α), $J_{4\alpha,4\beta}$=15.9, $J_{4\alpha,5}$=4.5), 2.71 (dd, 1H, H(4β), $J_{4\beta,4\alpha}$=15.9, $J_{4\beta,5}$=7.8), 3.41 (s, 2H, H(2α,2β)), 3.71 (m, 2H, H(9α,9β)), 3.77 (sex, 1H, H(7), $J_{7,8}$ = J_{7,CH_3} = 6.0), 3.97 (dddd, 1H, H(5), $J_{5,4\alpha}$=7.8, $J_{5,1'\alpha}$=6.6, $J_{5,4\beta}$=4.5,

$J_{5,1'\beta}$=4.6), 4.17 (q, 2H, OCH_2CH$_3$, J=7.2), 5.00–5.10 (m, 2H, H(3′)), 5.83 (ddt, 1H, H(2′) $J_{2',3'\text{trans}}$=17.5, $J_{2',3'\text{cis}}$=9.7, $J_{2',1'}$=7.2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 19.5, 38.3, 39.2, 47.6, 50.6, 60.5, 61.2, 72.0, 72.6, 118.4, 133.5, 166.9, 201.6; MS (EI, 70 eV, 30 °C): m/z (%)=273 (100, M+H$^+$), 231 (36).

4.4. (5*R*)-Ethyl 5-hydroxy-3-oxooct-7-enoate (3)

To **2** (452 mg, 1.66 mmol) dissolved in dry dichloromethane (20 mL), Dess–Martin periodinane (783 mg, 1.84 mmol) was added and the reaction mixture stirred under argon at room temperature for 1 h. A solution of $NaHCO_3$ (3 g) and $Na_2S_2O_3$ (3 g) in 10 mL water was added and the mixture stirred at room temperature for 40 min. The aq layer was extracted several times with dichloromethane and the combined organic layers were extracted with satd aq $NaHCO_3$ (2×) and brine (2×), and dried (Na_2SO_4). The solvent was removed under reduced pressure yielding the crude aldehyde (450 mg, 0.83 mmol), which was immediately dissolved in dry benzene and cooled to 6 °C under argon. Dibenzylammonium trifluoroacetate (530 mg, 0.89 mmol) was added and the mixture stirred for 90 min. Then ethyl acetate (10 mL) and water (10 mL) were added and the aq layer extracted with ethyl acetate. The combined organic layers were extracted with aq 1 N HCl (2×), aq satd $NaHCO_3$ (2×) and brine (2×), and dried (Na_2SO_4). The solvent was removed under reduced pressure yielding an orange-red oil (398 mg). Part of this product was purified by flash chromatography on silica gel (dichloromethane/methanol 200:1) whereas the main product was used without further purification in the next step. $[\alpha]_D^{20}$ −35.35 (c 0.22, $CHCl_3$). IR (cm^{-1}, film): 3519 (br), 3075, 2983, 2926, 1732, 1714, 1643, 1370; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.21 (t, 3H, CH_3, J_{CH_3,CH_2} = 7.2), 2.20 (m, 2H, H(6), $J_{6,5}$∼$J_{6,7}$∼6.6, $J_{6,8}$∼1.3), 2.60 (dd, 1H, H(4α), $J_{4\alpha,4\beta}$∼17.7, $J_{4\alpha,5}$=8.5), 2.68 (dd, 1H, H(4β), $J_{4\beta,4\alpha}$∼17.7, $J_{4\beta,5}$=3.3), 2.72 (br, 1H, OH), 3.41 (s, 2H, H(2), 3.97 (dtd, 1H, H(5), $J_{5,4\alpha}$=8.5, $J_{5,6\alpha}$=6.4, $J_{5,6\beta}$=6.4, $J_{5,4\beta}$=3.3), 4.13 (q, 2H, OCH_2CH$_3$, J=7.2), 5.00–5.12 (m, 2H, H(8)), 5.74 (ddt, 1H, H(7), $J_{7,8\text{trans}}$=17.3, $J_{7,8\text{cis}}$=9.8, $J_{7,6}$=7.1); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 40.8, 48.8, 49.8, 61.4, 66.8, 118.2, 133.9, 166.9, 203.3; MS (EI, 70 eV, 30 °C): m/z (%)=200.8 (100, M+H$^+$), 159.1 (30).

4.5. (*R*)-6-Allyl-5,6-dihydro-3*H*-pyran-2,4-dione (4)

(a) To crude **3** (0.598 g, ∼2.98 mmol) dissolved in THF (9 mL) was added 1 N NaOH (3.28 mL, 3.28 mmol) dropwise at 5 °C and the mixture stirred at room temperature for 2 h. The organic solvent was removed under reduced pressure, water (30 mL) was added and the mixture was extracted with ethyl acetate (3×15 mL). The aq layer was acidified with $NaHSO_4$ and vigorously stirred at room temperature for 2 h and then extracted with ethyl acetate (6×15 mL). The combined organic layers were washed with brine (2×) and dried (Na_2SO_4), and the solvent removed under reduced pressure. Purification by flash chromatography on silica gel (dichloromethane/methanol 200:1) yielded **4** (130 mg, 0.84 mmol, 34% over two steps) as colourless crystals. Part of this product was recrystallized from petroleum ether/ethyl acetate. $[\alpha]_D^{20}$ −96.1 (c 0.36, CH_2Cl_2).

(b) Trifluoroacetic acid (1.14 g, 10 mmol) was added to a solution of β-keto ester (*R*)-**8** (2.3 g, 10 mmol) in dry dichloromethane (150 mL) under argon at 0 °C. The solution was stirred for 48 h at room temperature. Volatile materials were removed under reduced pressure and the crude product was purified by flash chromatography (petroleum ether/acetone 3:1, then petroleum ether/acetone/acetic acid 1:1:0.01) on silica gel and isolated as an oil, which solidified at 4 °C (1.37 g, 89%). $[\alpha]_D^{21}$ −95.3 (c 0.3, CH_2Cl_2). Mp=54–60 °C. IR (cm^{-1}, film): 3700–2460, 3079, 2923, 2852, 1729, 1668, 1278; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 2.43 (dt, 1H, H(1′α), $J_{1'\alpha.1'\beta}$=14.3, $J_{1'\alpha.2'}$∼$J_{1'\alpha.6}$∼6.4), 2.64 (dt, 1H, H(1′β), $J_{1'\alpha,1'\beta}$=14.3, $J_{1'\beta,2'}$∼$J_{1'\beta,6}$=6.4), 2.43 (dd, 1H, H(5ax), $J_{5,5}$=18.2, $J_{5,6}$=11.5), 2.65 (dd, 1H, H(5eq), $J_{5,5}$=18.3, $J_{5,6}$=2.8), 3.41 (d, 1H, H(3), $J_{3,3}$=18.9, with D_2O exchangeable), 3.55 (d, 1H, H(3), $J_{3,3}$=18.9, with D_2O exchangeable), 4.64 (ddt, 1H, H(6), $J_{6,5}$=11.6, $J_{6,1'\alpha}$=$J_{6,1'\beta}$=6.1, $J_{6,5}$=2.8), 5.16 (m, 2H, H(3′cis, 3′trans)), 5.76 (ddt, 1H, H(2′), $J_{2',3'\text{trans}}$=17.4, $J_{2',3'\text{cis}}$=9.6, $J_{2',1'}$=$J_{2',1'}$=7.1); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 38.5, 42.8, 47.0, 74.8, 120.0, 130.9, 167.1, 199.8; MS (EI, 70 eV, 30 °C): m/z (%)=154 (M$^+$, 9), 113 (87), 84 (62), 71 (100), 49 (66); HRMS (EI, 70 eV, 30 °C) calcd for $C_8H_{10}O_3$: 154.0630, found: 154.0628. Data for (*S*)-**4**: ee=99%. $[\alpha]_D^{20}$ +95.3 (c 0.9, CH_2Cl_2). Mp=52–59 °C.

4.6. (*R*)-6-Allyl-5,6-dihydro-4-methoxy-2*H*-pyran-2-one (5) and (*R*)-6-allyl-5,6-dihydro-2-methoxy-3*H*-pyran-2-one (6)

(a) To β-keto lactone (−)-**4** (230.6 mg, 1.5 mmol) dissolved in dry acetone (26 mL) were added K_2CO_3 (414.4 mg, 3.23 mmol) and dimethyl sulfate (0.28 mL, ∼3 mmol) and the reaction mixture was stirred at room temperature for 8.5 h. After removing the solvent under reduced pressure, water (25 mL) was added and extracted with ethyl acetate (4×). The combined organic layers were washed with brine (2×), dried with $MgSO_4$ and the solvent removed under reduced pressure. Purification by flash chromatography (petroleum ether/acetone 3:1) yielded **5** (175 mg, 1.04 mmol, 69%) as slightly coloured crystals and starting material (ca. 25 mg, 0.16 mmol, 10%).

(b) To β-keto lactone **4** (4.5 mg, 0.03 mmol) dissolved in dry diethyl ether (5 mL) was added a solution of diazomethane in diethyl ether dropwise until decolouration ceased. The mixture was stirred at room temperature for 3 h. After removal of the solvent under reduced pressure, the products were separated by flash chromatography (petroleum ether/acetone 3:1) yielding **5** (1.6 mg, 0.0095 mmol, 26%) and **6** (2 mg, 0.012 mmol, 40%) as colourless oil. Enol ether **5**: $[\alpha]_D^{20}$ −110.8 (c 1.245, acetone). Mp=35–41 °C. IR (cm^{-1}, film): 3080, 2918, 1702, 1651, 1624, 1390; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 2.31 (dd, 1H, H(5eq), $J_{5,5}$=17.2, $J_{5,6}$=3.9), 2.40–2.49 (m, 1H, H(1′α), 2.49 (ddd, 1H, H(5ax), $J_{5,5}$=17.2, $J_{5,6}$=12.3, $J_{5,3}$∼1.5), 2.55 (dddd, 1H, H(1′β), $J_{1'\beta,1'\alpha}$=14.3, $J_{1'\beta,2'}$=6.9, $J_{1'\beta,6}$=5.9, $J_{1'\beta,3'}$=1.5), 3.72 (s, 3H, OCH_3), 4.42 (dddd, 1H, H(6), $J_{6,5ax}$=12.3, $J_{6,1'\alpha}$=6.4, $J_{6,1'\beta}$=5.9, $J_{6,5eq}$=3.9), 5.12 (d, 1H, H(3), $J_{3,5ax}$=1.5), 5.00–5.12 (m, 2H, H(3′cis, 3′trans)), 5.82 (dddd, H(2′), $J_{2',3'\text{trans}}$=17.7, $J_{2',3'\text{cis}}$=9.4, $J_{2',1'\alpha}$∼$J_{2',1'\beta}$∼6.9–7.4); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 32.3, 38.9, 56.0, 75.1, 90.3, 119.0, 132.2, 167.1, 172.7; MS (EI, 70 eV, 30 °C):

m/z (%)=169 ($M+H^+$, 0.9), 127 (76), 95 (12), 72 (31), 67 (31), 59 (11); MS (FD, 20 °C) 168.5; HRMS (EI, 70 eV, 30 °C) calcd for $C_9H_{12}O_3$: 168.0786, found: 168.0790. Anal. Calcd for $C_9H_{12}O_3$: C=64.27%, H=7.19%; found: C=64.04%, H=7.21%. Methyl enolate **6**: IR (cm^{-1}, film): 2918, 2850, 1685, 1583, 1453; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 2.38 (dd, 1H, H(5eq), $J_{5,5}$=16.7, $J_{5,6}$=3.9), 2.49 (ddd, 1H, H(5ax), $J_{5,5}$=16.7, $J_{5,6}$=12.3), 2.49 (dddt, 1H, H(1′α), $J_{1',1'}$=15.3, $J_{1',2'}$=6.9, $J_{1',6}$=6.4, $J_{1',3'}$~1.3), 2.57 (dddt, 1H, H(1′β), $J_{1,1'}$=15.3, $J_{1',2'}$=6.9, $J_{1',6}$=6.4, $J_{1',3'}$~1.3), 3.76 (s, 3H, OCH_3), 4.54 (ddt, 1H, H(6), $J_{6,5ax}$~12.0, $J_{6,1'\alpha}=J_{6,1'\beta}$=6.4, $J_{6,5eq}$~4.1), 4.82 (s, 1H, H(3)), 5.14–5.21 (m, 2H, H(3′cis, 3′trans)), 5.80 (ddt, 1H, H(2′), $J_{2',3'trans}$=17.2, $J_{7,8cis}$=9.8, $J_{2',1'\alpha}=J_{2',1'\beta}$=6.9); ^{13}C NMR (100 MHz, $CDCl_3$) δ 38.4, 40.0, 55.7, 79.3, 82.5, 119.2, 131.7, 174.0, 192.2; MS (FD, 20 °C) 168.5.

4.7. (*R*)-*tert*-Butyl 5-hydroxy-3-oxoocto-7-enoate (8)[17]

LiHMDS (1 M in THF, 100 mL, 100 mmol) was added to dry THF (100 mL) under argon at −78 °C, followed by *tert*-butyl acetate (13.5 mL, 100 mmol). After 30 min at −78 °C, a solution of (*R*)-ethyl 3-hydroxyhex-5-enoate **7**[15] (3.95 g, 25 mmol) in dry THF (25 mL) was added to the reaction mixture, which was kept for further 30 min at −78 °C and then slowly warmed to −20 °C. A mixture of acetic acid (20 mL) and water (60 mL) was added and the aq phase was extracted with diethyl ether (3×). The organic extracts were washed with brine and dried ($MgSO_4$). After removal of the solvent under reduced pressure, the product was purified by flash chromatography on silica gel (petroleum ether/diethyl ether 1:1) and isolated as an oil (4.5 g, 78%). $[\alpha]_D^{20}$ −13.5 (*c* 0.9, acetone). IR (cm^{-1}, film): 3468, 3079, 2980, 2933, 1732, 1712, 1642, 1370, 1325, 1257, 1150; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.48 (s, 9H, $(CH_3)_3C$), 2.27 (m, 1H, H(6α), $J_{6,6}$=13.9, $J_{6,7}$=7.1, $J_{6,5}$=6.1, $J_{6,8}$~$J_{6,8}$~1.7), 2.29 (m, 1H, H(6β), $J_{6,6}$=13.9, $J_{6,7}$~$J_{6,5}$~6.8, $J_{6,8}$~$J_{6,8}$~1.7), 2.66 (dd, 1H, H(4α), $J_{4,4}$=17.5, $J_{4,5}$=3.3), 2.75 (dd, 1H, H(4β), $J_{4,4}$=17.5, $J_{4,5}$=8.7), 2.83 (br s, 1H, OH), 3.39 (AB-system, 2H, H(2,2), $J_{2,2}$=15.7), 4.16 (m, 1H, H(5), $J_{5,4\beta}$=8.8, $J_{5,6\alpha}$~$J_{5,6\beta}$~6.1, $J_{5,4\alpha}$=3.3), 5.14 (m, 2H, H(8cis,8trans)), 5.83 (ddt, 1H, H(7), $J_{7,8trans}$=17.3, $J_{7,8cis}$=9.9, $J_{7,6\alpha}=J_{7,6\beta}$=7.2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.9, 40.9, 48.7, 51.2, 66.8, 82.2, 118.2, 134.0, 166.1, 203.9; MS (EI, 70 eV, 30 °C): *m/z* (%)=172 (3), 155 (11), 131 (65), 113 (28), 71 (42), 57 (100); Data for (*S*)-**8**: ee=99%. $[\alpha]_D^{20}$ +13.4 (*c* 0.9, acetone).

4.8. (3*S*)-4-(*tert*-Butyldiphenylsiloxy)-3-(4-methoxybenzyloxy)-butanol (10)

To a suspension of $LiAlH_4$ (54 mg, 1.42 mmol) in dry THF (3 mL) was dropped slowly a solution of **9**[49] (635 mg, 1.29 mmol) in dry THF (5 mL) under argon at 0 °C. The reaction was quenched after 75 min with a satd aq solution of NH_4Cl (5 mL). The mixture was extracted with diethyl ether (3×). The combined organic phases were washed with brine and dried ($MgSO_4$). After removal of the solvent under reduced pressure, the crude product was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate 2:1) affording the product as a colourless viscous oil (463 mg, 77%). The analytical data are in agreement with the literature.[50]

4.9. (3*S*)-4-(*tert*-Butyldiphenylsiloxy)-3-(4-methoxybenzyloxy)butanal (11)[19]

A solution of **10** (0.43 g, 0.93 mmol) in dry dichloromethane (5 mL) was added to a suspension of Dess–Martin periodinane (0.43 g, 1.02 mmol) in dry dichloromethane (10 mL). The reaction mixture was stirred under argon at room temperature for 50 min and then quenched with satd aq $NaHCO_3$ (10 mL) containing $Na_2S_2O_3\cdot 5H_2O$ (1.9 g). The aq phase was separated and extracted with diethyl ether. The combined organic phases were dried ($MgSO_4$) and after removal of the solvent under reduced pressure, the crude product was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate 2:1). The product was isolated as colourless viscous oil (0.39 g, 91%). The analytical data agreed with the literature.[19]

4.10. (3*R*,5*S*)-6-(*tert*-Butyldiphenylsiloxy)-3-hydroxy-1-[(4′*R*)-4′-isopropyl-2′-thioxothiazolidin-3′-yl]-4-(4-methoxybenzyloxy)-hexan-1-one (12) and (3*S*,5*S*)-6-(*tert*-butyldiphenylsiloxy)-3-hydroxy-1-[(4′*R*)-4′-isopropyl-2′-thioxothiazolidin-3′-yl]-4-(4-methoxybenzyloxy)-hexan-1-one (13)[51]

To a suspension of freshly dried $Sn(OTf)_2$ (2.81 g, 6.74 mmol) in dry dichloromethane (5.5 mL) were added slowly at −50 °C under argon *N*-ethylpiperidine (0.93 mL, 6.74 mmol) and a solution of (4*R*)-*N*-acetyl-4-isopropyl-1,3-thiazolidin-2-thione[21] (1.14 g, 5.61 mmol) in dry dichloromethane (1.5 mL). After 4 h, the reaction mixture was cooled to −78 °C and a solution of aldehyde **11** (2.98 g, 6.44 mmol) in dry dichloromethane (6 mL) was added slowly. After a further 7 h, the reaction was quenched with a solution (50 mL) of Na_2HPO_4 (450 mg) and KH_2PO_4 (110 mg) dissolved in water (50 mL), and the mixture was allowed to warm to room temperature. Solids were removed by filtration through Celite and washed with ethyl acetate. The organic layer was separated and the aq phase extracted with ethyl acetate. The combined organic phases were dried (Na_2SO_4) and the solvent removed under reduced pressure. The crude mixture of diastereomers was separated by flash chromatography on silica gel (petroleum ether/ethyl acetate 3:1). The products were isolated as yellow, viscous oils. Major product **12**: 2.83 g (76%). $[\alpha]_D^{20}$ −161.4 (*c* 1.0, acetone). IR (cm^{-1}, film): 3468, 2960, 1697, 1612, 1514, 1471, 1428, 1363, 1304, 1249, 1166, 1113, 1038; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 0.98 (d, 3H, CH_3, $J_{CH_3,1''}$ = 6.8), 1.07 (s, 9H, $(CH_3)_3C$)), ~1.06 (d, 3H, CH_3), 1.78 (m, 1H, H(4α), $J_{4,4}$=14.4, $J_{4,5}$~$J_{4,3}$~7.8), 1.81 (m, 1H, H(4β), $J_{4,4}$=14.6, $J_{4,5}$~$J_{4,3}$~4.55), 2.36 (oct., 1H, H(1″), *J*~6.8), 3.01 (dd, 1H, H(5′α), $J_{5',5'}$=11.5, $J_{5',4'}$~0.9), 3.28 (dd, 1H, H(2α), $J_{2,2}$=17.4, $J_{2,3}$~8.5), 3.42 (dd, 1H, H(2β), $J_{2,2}$=17.4, $J_{2,3}$=3.3), 3.49 (dd, 1H, H(5′β), $J_{5',5'}$=11.4, $J_{5',4'}$=7.8), 3.52 (s, 1H, OH), 3.68 (dd, 1H, H(6α), $J_{6,6}$=9.85, $J_{6,5}$=3.3), 3.74 (m, 1H, H(5), $J_{5,4\alpha}$~7.8, $J_{5,4\beta}$~$J_{5,6\beta}$~4.55, $J_{5,6\alpha}$=3.3), 3.79 (dd, 1H, H(6β), $J_{6,6}$=9.85, $J_{6,5}$=4.55), 3.79 (s, 3H, CH_3O), 4.35 (m, 1H, H(3)), 4.39 (dd, 1H, OCH_2Ar, *J*=11.1), 4.60 (d, 1H, OCH_2Ar, *J*=11.1), 5.14 (m, 1H, H(4′), $J_{4',5'}$~$J_{4',1''}$~6.7, $J_{4',5'}$~0.9), 6.84 (m, 2H, Ar), 7.19 (m, 2H, Ar), 7.41 (m, 6H, Ar), 7.68 (m, 4H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 17.8, 19.1, 19.2, 26.85, 30.6, 30.9, 38.3, 45.6, 55.2, 65.8, 66.9, 71.5, 71.6, 78.7, 113.8, 127.7, 127.75, 129.4, 129.7, 130.2, 133.2,

133.3, 135.6, 135.6, 159.2, 172.3, 202.8. Minor product **13**: 173 mg (4.6%). $[\alpha]_D^{20}$ −144.5 (*c* 0.3, acetone). IR (cm^{-1}, film): 3545, 2960, 2859, 1686, 1612, 1587, 1560, 1514, 1466, 1428, 1363, 1248, 1165, 1113, 1038; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 0.98 (d, 3H, CH_3, $J_{CH_{3,1''}}=7.1$), 1.07 (d, 3H, CH_3, $J_{CH_{3,1''}}=7.1$), 1.08 (s, 9H, $(CH_3)_3C$)), 1.65 (ddd, 1H, H(4α), $J_{4,4}$=14.3, $J_{4,5}$=9.1, $J_{4,3}$=3.0), 1.75 (ddd, 1H, H(4β), $J_{4,4}$=14.3, $J_{4,3}$=9.4, $J_{4,5}$=3.2), 2.37 (oct., 1H, H(1″), J=6.8), 3.02 (dd, 1H, H(5′trans), $J_{5',5'}$=11.6, $J_{5',4'}$=1.0), 3.295 (dd, 1H, H(2α), $J_{2,2}$=17.2, $J_{2,3}$=3.1), 3.30 (br d, 1H, OH, $J_{OH,3}$=4.3), 3.49 (dd, 1H, H(2β), $J_{2,2}$=17.2, $J_{2,3}$=9.1), 3.50 (dd, 1H, H(5′cis), $J_{5',5'}$=11.6, $J_{5',4'}$=7.8), 3.67 (dd, 1H, H(6α), $J_{6,6}$=10.6, $J_{6,5}$=5.2), 3.75 (dd, 1H, H(6β), $J_{6,6}$=10.6, $J_{6,5}$=5.6), 3.80 (s, 3H, OMe), 3.84 (m, 1H, H(5), $J_{5,4\alpha}$=9.1, $J_{5,6\alpha}$=5.6, $J_{5,6\beta}$=5.2, $J_{5,4\beta}$=3.2), 4.30 (m, 1H, H(3)), 4.44 (dd, 1H, OCH_2Ar, J=11.1), 4.63 (dd, 1H, OCH_2Ar, J=11.1), 5.14 (m, 1H, H(4′), $J_{4',5'}\sim J_{4',1''}\sim$7.1, $J_{4',5'}\sim$1), 6.85 (m, 2H, Ar), 7.22 (m, 2H, Ar), 7.40 (m, 6H, Ar), 7.69 (m, 4H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.7, 19.1, 19.2, 26.85, 30.5, 30.75, 38.6, 45.6, 55.3, 65.3, 66.4, 71.4, 72.3, 76.5, 113.8, 127.7, 129.5, 129.7, 130.8, 133.4, 133.4, 135.6, 159.1, 173.15, 202.9.

4.11. Ethyl (3*R*,5*S*)-6-(*tert*-butyldiphenylsiloxy)-3-hydroxy-5-(*p*-methoxybenzyloxy)hexanoate (14)[52]

To a yellow solution of **12** (2.45 g, 3.68 mmol) in dry ethanol (25 mL) was added DMAP (90 mg, 0.74 mmol). The solution was stirred under argon overnight and became colourless. After removal of the solvent under reduced pressure, the product was separated from the chiral auxiliary by flash chromatography on silica gel (toluene/dichloromethane 1:1, petroleum ether/ethyl acetate 2:1) giving chiral auxiliary (551 mg, 93%) and product (1.99 g, 98%) as colourless, viscous oil. $[\alpha]_D^{20}$ −18.1 (*c* 1.0, acetone). IR (cm^{-1}, film): 3503, 3070, 2931, 2858, 1734, 1612, 1587, 1514, 1472, 1428, 1390, 1371, 1302, 1249, 1174, 1113, 1036; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.08 (s, 9H, $(CH_3)_3C$), 1.27 (t, 3H, CH_3CH_2O, $J_{CH_3,CH_2}=7.2$), 1.75 (m, 1H, H(4α), $J_{4,4}$=14.4, $J_{4,5}\sim J_{4,3}\sim$8.4), 1.79 (m, 1H, H(4β), $J_{4,4}$=14.6, $J_{4,5}\sim J_{4,3}\sim$4.3), 2.37 (dd, 1H, H(2α), $J_{2,2}$=15.7, $J_{2,3}$=5.1), 2.46 (dd, 1H, H(2β), $J_{2,2}$=15.7, $J_{2,3}$=7.8), 3.68 (dd, 1H, H(6α), $J_{6,6}$=9.6, $J_{6,5}$=4.3), ∼3.74 (m, 1H, H(5)), 3.79 (dd, 1H, H(6β), $J_{6,6}$=9.6, $J_{6,5}$=4.3), 3.80 (s, 3H, CH_3O), 4.16 (q, 2H, CH_3CH_2O, J_{CH_2,CH_3}= 7.2), 4.21 (m, 1H, H(3)), 4.40 (d, 1H, OCH_2Ar, J=11.1), 4.62 (d, 1H, OCH_2Ar, J=11.1), 6.85 (m, 2H, Ar), 7.20 (m, 2H, Ar), 7.34–7.49 (m, 6H, Ar), 7.69 (m, 4H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 14.2, 19.2, 26.8, 38.25, 41.9, 55.2, 60.5, 65.8, 67.2, 71.6, 78.7, 113.85, 127.7, 127.75, 129.5, 129.8, 130.2, 133.2, 133.3, 135.6, 135.6, 159.3, 172.1; HRMS (EI, 70 eV, 140 °C) calcd for $C_{28}H_{33}O_6Si$ $(M-t\text{-}Bu)^+$: 493.2046, found: 493.2054.

4.12. Ethyl (3*S*,5*S*)-6-(*tert*-butyldiphenylsiloxy)-3-hydroxy-5-(4-methoxybenzyloxy)hexanoate (13a)

Compound **13** (134 mg, 0.201 mmol) was transformed in the same way as **12** giving chiral auxiliary quantitatively and product **13a** (96 mg, 87%) as a colourless viscous oil. $[\alpha]_D^{20}$ −26.1 (*c* 1.0, acetone). IR (cm^{-1}, film): 3504, 3071, 2932, 2858, 1732, 1613, 1588, 1514, 1471, 1443, 1428, 1391, 1373, 1348, 1302, 1248, 1174, 1112, 1036; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.08 (s, 9H, $(CH_3)_3C$), 1.27 (t, 3H, CH_3CH_2O, J=7.2), 1.66 (ddd, 1H, H(4α), $J_{4,4}$=14.3, J∼8.2, J=3.3), 1.75 (ddd, 1H, H(4β), $J_{4,4}$=14.3, J=8.9, J∼3.5), 2.45 (m, 2H, H(2α,2β)), 3.2 (br s, 1H, OH), 3.70 (dd, 1H, H(6α), $J_{6,6}$=10.4, $J_{6,5}$=5.1), 3.78 (dd, 1H, H(6β), $J_{6,6}$=10.4, $J_{6,5}$=5.3), 3.80 (s, 3H, CH_3O), ∼3.84 (m, 1H, H(5)), 4.17 (q, 2H, CH_3CH_2, $J_{CH_2,CH_3}=7.1$), 4.27 (m, 1H, H(3)), 4.46 (d, 1H, OCH_2Ar, J=11.1), 4.64 (d 1H, OCH_2Ar, J=11.1), 6.86 (m, 2H, Ar), 7.24 (m, 2H,Ar), 7.34–7.51 (m, 6H, Ar), 7.70 (m, 4H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 14.15, 19.2, 26.8, 38.35, 41.9, 55.2, 60.5, 65.0, 66.2, 72.2, 76.4, 113.8, 127.7, 129.5, 129.7, 130.6, 133.3, 133.4, 135.6, 159.2, 172.5; HRMS (EI, 70 eV, 140 °C) calcd for $C_{28}H_{33}O_6Si$ $(M-t\text{-}Bu)^+$: 493.2046, found: 493.2057.

4.13. (5*R*,7*S*)-*tert*-Butyl 8-(*tert*-butyldiphenylsiloxy)-5-hydroxy-7-(4-methoxybenzyloxy)-3-oxooctanoate (15)[17]

LiHMDS (1 M in THF, 13.5 mL, 13.5 mmol) was added to dry THF (10 mL) under argon at −78 °C, followed by *tert*-butyl acetate (1.8 mL, 13.5 mmol). After 30 min at −78 °C, a solution of **14** (1,49 g, 2.7 mmol) in dry THF (15 mL) was added to the reaction mixture, which was kept for a further 30 min at −78 °C and then slowly warmed to 0 °C. A mixture of acetic acid (3 mL) and water (9 mL) was added and the aq phase was extracted with diethyl ether (3×). The organic extracts were washed with brine and dried ($MgSO_4$). After removal of the solvent under reduced pressure, the product was purified by flash chromatography on silica gel (petroleum ether/diethyl ether 1:1) and isolated as an oil (1.59 g, 87%) that contained 10 mol % of the starting material. An analytically pure sample was obtained by renewed flash chromatography, which was an ∼8:1 mixture of ketone/enol. $[\alpha]_D^{20}$ −20.0 (*c* 0.7, acetone). IR (cm^{-1}, film): 3502, 2931, 2859, 1734, 1713, 1612, 1588, 1514, 1472, 1428, 1392, 1368, 1303, 1250, 1147, 1113, 1036; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.07 (s, 9H, $(CH_3)_3CSi$), 1.46 (s, 9H, $(CH_3)_3CO$), 1.72 (m, 2H, H(6α,6β)), 2.55 (dd, 1H, H(4α), $J_{4,4}$=16.7, $J_{4,5}$=4.5), 2.67 (dd, 1H, H(4β), $J_{4,4}$=16.7, $J_{4,5}$=7.6), 3.36 (s, 2H, H(2α,2β)), 3.57–3.80 (m, 4H, H(8α,8β,7), OH), 3.80 (s, 3H, CH_3O), 4.22 (m, 1H, H(5)), 4.38 (d, 1H, OCH_2Ar, J=11.1), 4.61 (d, 1H, OCH_2Ar, J=11.1), 6.84 (m, 2H, Ar), 7.19 (m, 2H, Ar), 7.33–7.50 (m, 6H, Ar), 7.68 (m, 4H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.2, 26.8, 28.0, 38.2, 49.9, 51.25, 55.25, 65.8, 66.8, 71.6, 78.8, 82.0, 113.9, 127.7, 127.8, 129.5, 129.8, 130.15, 133.2, 133.3, 135.6, 135.6, 159.3, 166.3, 202.9.

4.14. (6*R*,2′*S*)-6-[3′-*tert*-Butyldiphenylsiloxy-2′-(4-methoxybenzyloxy)prop-1′-yl]-5,6-dihydro-4-hydroxy-2*H*-pyran-2-one (16)[53]

A solution of trifluoroacetic acid in dry dichloromethane (0.9 M, 4.2 mL, 0.38 mmol) was added to **15** (689 mg, 1.11 mmol). The solution was stirred under argon at room temperature for 4 days and then directly used for flash chromatography (petroleum ether/acetone 3:1) giving recovered starting material (284 mg, 41%) and product, which was isolated as an oil that solidified at 4 °C (288 mg, 47%). $[\alpha]_D^{20}$ −52.7 (*c* 0.7, acetone). IR (cm^{-1}, film): 1729, 1668,

1621, 1278, 1221, 1041; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.08 (s, 9H, $(CH_3)_3C$), 1.91 (m, 1H, H(1′α), $J_{1',1'}$= 14.1, $J_{1',6}$=7.6, $J_{1',2'}$=4.5), 2.14 (m, 1H, H(1′β), $J_{1',1'}$=14.1, $J_{1',2'}$=8.2, $J_{1',6}$=5.8), 2.25 (m, 1H, H(5ax), $J_{5,5}$=18.4, $J_{5,6}$=10.3), 2.32 (m, 1H, H(5eq), $J_{5,5}$=18.4, $J_{5,6}$=3.8), 3.33 (d, 1H, H(3α), $J_{3,3}$=18.7), 3.37 (d, 1H, H(3β), $J_{3,3}$=18.7), 3.55 (m, 1H, H(2′), $J_{2',1'\beta}$=8.2, $J_{2',1'\alpha}$∼$J_{2',3'\beta}$∼ 4.5, $J_{2',3'\alpha}$=5.4), 3.72 (dd, 1H, H(3′α), $J_{3',3'}$=10.7, $J_{3',2'}$= 5.4), 3.80 (dd, 1H, H(3′β), $J_{3',3'}$∼10.1, $J_{3',2'}$=4.5), 3.80 (s, 3H, CH_3O), 4.28 (d, 1H, OCH_2Ar, J=11.6), 4.55 (d, 1H, OCH_2Ar, J=11.6), 4.57 (m, 1H, H(6)), 6.85 (m, 2H, Ar), 7.16 (m, 2H,Ar), 7.33–7.50 (m, 6H,Ar), 7.67 (m, 4H,Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 19.2, 26.9, 36.6, 43.0, 47.05, 55.3, 65.2, 71.4, 73.0, 74.2, 113.9, 127.8, 127.8, 129.7, 129.9, 129.9, 130.45, 133.1, 133.2, 135.6, 135.6, 159.5, 167.1, 199.8; HRMS (EI, 70 eV, 130 °C) calcd for $C_{28}H_{29}O_6Si$ (M−*t*-Bu)$^+$: 489.1733, found: 489.1724.

4.15. (2′*S*,4′*R*,6′*S*)-Ethyl {[6′-(*tert*-butyldiphenylsiloxy)-methyl]-2′-(4-methoxyphenyl)-1′,3′-dioxan-4′-yl}acetate (17)[22]

To a mixture of a solution of **14** (180 mg, 0.327 mmol) in dichloromethane (10 mL) and water (1 mL) was added 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (111 mg, 0.49 mmol) at 0 °C. The reaction mixture was stirred for 1.5 h at room temperature and then quenched with a satd aq solution of $NaHCO_3$ (5 mL). The organic phase was removed and the aq phase extracted with dichloromethane (2×). The combined organic phases were washed with brine and dried (Na_2SO_4). After removal of the solvent under reduced pressure the crude product was purified by flash chromatography on silica gel (petroleum ether/diethyl ether 3:1) and isolated as a viscous oil (137 mg, 76%). $[\alpha]_D^{20}$ −8.5 (*c* 0.5, acetone). IR (cm^{-1}, film): 2931, 1736, 1616, 1518, 1428, 1344, 1303, 1250, 1172, 1113, 1032; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.08 (s, 9H, $(CH_3)_3C$)), 1.28 (t, 3H, CH_3CH_2O, J=7.2), 1.51 (dt, 1H, H(5′ax), $J_{5',5'}$=12.9, $J_{5',4'}$=$J_{5',6'}$= 11.4), 1.82 (dt, 1H, H(5′eq), $J_{5',5'}$=13.0, $J_{5',4'}$=$J_{5',6'}$=2.3), 2.53 (dd, 1H, H(2α), $J_{2,2}$=15.5, $J_{2,4'}$=5.9), 2.74 (dd, 1H, H(2β), $J_{2,2}$=15.5, $J_{2,4'}$=7.2), 3.71 (dd, 1H, H(1″α), $J_{1'',1''}$= 10.5, $J_{1'',6'}$=5.4), 3.81 (s, 3H, OCH_3)), 3.87 (dd, 1H, H(1″β), $J_{1'',1''}$=10.6, $J_{1'',6'}$=5.3), 4.06 (m, 1H, H(6′), $J_{6',5'}$= 11.4, $J_{6',1''\alpha}$=$J_{6',1''\beta}$=5.4, $J_{6',5'}$=2.3), 4.18 (q, 2H, CH_3CH_2O, J_{CH_3,CH_2} = 7.2), 4.34 (m, 1H, H(4′), $J_{4',5'ax}$=11.4, $J_{4',2\beta}$=7.2, $J_{4',2\alpha}$=5.9, $J_{4',5'}$=2.3), 5.54 (s, 1H, H(2′)), 6.88 (m, 2H, Ar), 7.40 (m, 8H, Ar), 7.71 (m, 4H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 14.20, 19.3, 26.8, 33.1, 41.15, 55.3, 60.5, 66.7, 73.2, 76.9, 100.5, 113.45, 127.4, 127.6, 129.6, 131.0, 133.5, 135.6, 135.6, 159.8, 170.7; HRMS (EI, 70 eV, 30 °C) calcd for $C_{28}H_{31}O_6Si$ (M−*t*-Bu)$^+$: 491.1890, found: 491.1881. NOE crosspeaks 2′/4′, 2′/6′ and 4′/6′ establish the equatorial position of all substituents and thus the desired relative and absolute configurations of the two stereogenic centres of the hexanoate **14**.

4.16. (1*R*,2*S*,6*S*,7*S*,8*S*)-7-Acetoxy-2-formyl-8-methylbicyclo[4.3.0]non-3-ene (18)

To a solution of (1*R*,2*S*,6*S*,7*S*,8*S*)-7-acetoxy-8-methyl-2-hydroxymethylbicyclo[4.3.0]non-3-ene[4d] (13.1 mg, 0.045 mmol) in dry dichloromethane (6 mL) were added $NaHCO_3$ and freshly prepared Dess–Martin periodinane (60 mg, 0.14 mmol) under an argon atmosphere and stirred rapidly at room temperature. After starting material was consumed (usually <1 h), the reaction was quenched with a 3:1 mixture (5 mL) of satd aq $Na_2S_2O_3$ solution and satd aq $NaHCO_3$ solution. The mixture was extracted with dichloromethane (4×) and the combined organic layers were dried ($MgSO_4$). The solvent was removed by rotary evaporation, and the residue was dried under vacuum and used without further purification. Usually the crude aldehyde (**18**) contained ca. 5% impurities. This aldehyde is unstable on silica gel. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 0.91 (d, 3H, CH_3(8), $J_{CH_{3,8}}$ = 7.1), 1.6 (dt, 1H, H(9), $J_{9,9}$=13.1, $J_{9,8}$∼$J_{9,1}$∼7.3), 1.81 (ddd, 1H, H(9), $J_{9,9}$=13.1, $J_{9,8}$∼8.6, $J_{9,1}$∼5.8), 1.87 (m, 1H, H(5)), 2.07 (s, 3H, CH_3CO), 2.19–2.28 (m, 2H, H(5,6)), 2.46 (m, 1H, H(8), J_{8,CH_3}∼$J_{8,9}$∼$J_{8,7}$∼7.1, $J_{8,9}$= 8.5), 2.56 (m, 1H, H(1), $J_{1,6}$∼$J_{1,2}$∼8.8, $J_{1,9}$∼7.3, $J_{1,9}$∼5.8), 2.785 (m, 1H, H(2), $J_{2,1}$∼8.8, $J_{2,3}$∼4.0, $J_{2,4}$∼$J_{2,1'}$∼$J_{2,5}$∼2), 4.87 (dd, 1H, H(7), $J_{7,8}$=6.9, $J_{7,6}$=5.1), 5.77 (m, 1H, H(3), $J_{3,4}$=10.1, $J_{3,2}$=3.9, $J_{3,5}$∼$J_{3,5}$∼1.9), 5.98 (m, 1H, H(4), $J_{4,3}$= 10.1, $J_{4,5}$∼$J_{4,5}$∼4.0, $J_{4,2}$=2.3), 9.58 (d, 1H, H(1′), $J_{1',2}$=1.8); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 15.5, 21.4, 25.0, 33.1, 33.4, 38.2, 40.65, 51.7, 81.5, 121.0, 130.2, 171.3, 201.1.

4.17. 4-(Bis(6-allyl-2,4-dioxo-tetrahydro-2*H*-pyran-3-yl)methyl)-2-methyl-2,3,3a,4,7,7a-hexahydro-1*H*-inden-1-yl acetate (20)

A solution of the crude aldehyde **18** (18.5 mg, 83 μmol) in carbon disulfide (0.3 mL) and dry DMF (0.1 mL) was cooled to −25 °C and treated with β-keto lactone **4** (13.8 mg, 89 μmol). The reaction was stirred overnight at −25 °C then quenched with satd aq NH_4Cl, extracted with diethyl ether, washed with brine and dried (Na_2SO_4). The solvent was removed under reduced pressure and the crude product purified by flash chromatography on silica gel (petroleum ether/acetone 3:1) yielding 4 mg of compound **20** (17%). IR=3300 (v br), 2924, 1732, 1652, 1645, 1391, 1246; ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 0.87 (d, 3H, CH_3(2), $J_{CH_{3,2}}$ = 7.1), 1.43 (ddd, 1H, H(3), $J_{3,3a}$=5.6, $J_{3,2}$=8.2, $J_{3,3}$=12.9), 1.62 (dt, 1H, H(3), $J_{3,2}$=$J_{3,3a}$=9.5, $J_{3,3}$=12.9), 1.67 (m, 1H, H(7), $J_{7,7}$=18.3), 2.00 (s, 3H, CH_3CO), 2.11 (m, 1H, H(7a)), 2.18 (m, 2H, H(3a,7)), 2.39 (m, 1H, H(2)), 2.43 (dd, 1H, H(5″), $J_{5'',5''}$=17.9, $J_{5'',6''}$=3.4), 2.455 (dd, 1H, H(5′), $J_{5',5'}$=17.9, $J_{5',6'}$=3.5), 2.47–2.62 (m, 4H, allylic H(1)), 2.53 (dd, 1H, H(5″), $J_{5'',5''}$=17.9, $J_{5'',6''}$=13.3), 2.57 (dd, 1H, H(5′), $J_{5',5'}$=17.9, $J_{5',6'}$=13.2), 3.12 (m, 1H, H(4), $J_{4,5}$=4.3, $J_{4,3a}$=11.9), 3.51 (d, 1H, methine–H, $J_{H,4}$=11.9), 4.36 (m, 1H, H(6′)), 4.38 (m, 1H, H(6″), J=3,5, J=6.1, J= 6.15, $J_{6'',5''}$=13.2), 4.89 (dd, 1H, H(1), J=2.4, J=5.8), 5.19 (m, 4H, allylic H(3)), 5.67 (m, 1H, H(5), $J_{5,6}$=10.2, $J_{5,4}$= 4.8, $J_{5,7}$∼$J_{5,7}$∼0.5–1.5), 5.69 (m, 1H, H(6), $J_{6,5}$=10.2, $J_{6,7}$=$J_{6,7}$=3.5, $J_{6,4}$∼0.4), 5.823 and 5.824 (m, 2H, allylic H(2), $J_{2,3}$∼17.1, $J_{2,3}$∼10.3, $J_{2,1}$∼$J_{2,1}$=7.1), 11.54 (br s, 1H, OH), 12.17 (br s, 1H, OH). ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) 15.0, 21.0, 24.3, 33.4, 33.7, 34.02, 34.03, 37.1, 37.5, 37.7, 38.4, 38.5, 39.3, 75.4, 75.8, 82.4, 103.7, 104.0, 119.3, 119.45, 127.0, 128.0, 131.5, 131.7, 170.1, 170.5, 171.7, 172.5, 174.8; ^{1}H NMR (600 MHz, C_6D_6) δ (ppm) 0.87 (d, 3H, CH_3(2), $J_{CH_{3,2}}$=7.1), 1.43–1.49 (m, 2H, H(3,7)), 1.625 (dt, 1H, H(3), $J_{3,2}$=$J_{3,3a}$=9.3, $J_{3,3}$=13), 1.72 (s, 3H, CH_3CO), 1.85–2.08 (m, 9H, 4×allylic H(1), 2×H(5′), 2×H(5″), H(7)), 2.17 (m, 1H, H(2)), 2.18 (m, 1H, H(7a)), 2.42 (m, 1H, H(3a), $J_{3a,3}$∼$J_{3a,3}$∼$J_{3a,4}$=8.3),

3.49 (m, 1H, H(4), $J_{4,5}$=4.7, $J_{4,3a}$=12.0), 3.86 (m, 1H, H(6′), J=3,8, J=6.1, $J_{6'',5''}$=13.1), 3.90 (d, 1H, methine–H, $J_{H,4}$= 11.9), 4.09 (m, 1H, H(6″), $J_{6'',5''}$∼$J_{6'',ally''1}$∼$J_{6'',ally''1}$∼6.1, $J_{6'',5''}$=10.9), 4.82–4.91 (m, 4H, allylic H(3)), 5.035 (dd, 1H, H(1), J=2.3, 5.7), 5.45 (m, 1H, allylic H(2), $J_{2,3}$∼17.1, $J_{2,3}$∼10.2, $J_{2,1}$∼$J_{2,1}$=7.1), 5.475 (m, 1H, allylic H(2), $J_{2,3}$∼17.1, $J_{2,3}$∼10.2, $J_{2,1}$∼$J_{2,1}$=7), 5.65 (m, 1H, H(6), $J_{6,5}$=10.1, $J_{6,7}$=$J_{6,7}$=4.1, $J_{6,4}$∼1), 5.87 (m, 1H, H(5), $J_{5,6}$=10.1, $J_{5,4}$=4.25, $J_{5,7}$∼$J_{5,7}$∼2.1, J∼1); ^{13}C NMR (150 MHz, C_6D_6) δ (ppm) 15.2, 20.8, 24.7, 33.7, 34.05, 34.4, 34.6, 37.9, 38.1, 38.4, 38.5, 38.7, 40.3, 75.2, 75.7, 82.6, 104.3, 104.6, 118.7, 118.8, 127.4, 128.6, 132.15, 132.3, 169.6, 170.5, 172.2, 172.8, 175.1; MS (EI, 70 eV, 120 °C): *m/z* (%) 512 (∼1), 343 (3), 319 (6), 308 (2), 298 (3), 131 (4), 121 (16), 84 (100); HRMS (EI, 70 eV, 30 °C) calcd for $C_{29}H_{36}O_8$: 512.2401, found: 512.2393.

4.18. (2*S*/2*R*,4*S*/4*R*,7*R*,1′*R*,2′*R*,3a′*S*,4′*S*,7a′*R*)-7-Allyl-2-methoxy-2-methyl-4-[1′-(triethylsiloxy)-2′-methyl-2′,3′,3a′,4′,7′,7a′-hexahydro-1*H*-inden-4′-yl]-3,4,7,8-tetrahydro-2*H*,5*H*-pyrano[4,3-*b*]pyran-5-one (22)

(*R*)-6-Allyldihydropyran-2,4-dione **4** (28 mg, 0.17 mmol) and EDDA (7.5 mg, 41 μmol) were dissolved in a mixture of 2-methoxypropene (5 mL), dry DMF (2.5 mL) and dry dichloromethane (2.5 mL), and cooled to −40 °C. A solution of crude **21**[4e] (ca. 60 mg, 0.20 mmol) in dry dichloromethane (2.5 mL) was added by syringe. The solution was stirred for 3 h, maintaining the temperature in the range of −30 to −40 °C, then allowed to warm to room temperature. [Alternatively, the reaction mixture was left in the freezer (−28 °C) overnight with no apparent effect on the yield.] The mixture was diluted with water (15 mL), extracted with EtOAc (3×15 mL) and the combined organic layers were dried over $MgSO_4$. The product can be purified by flash chromatography (silica gel, petroleum ether/ethyl acetate 5:1), but the diastereomers were inseparable and material was lost on the column. Therefore, the crude product was generally hydrolyzed without purification. NMR signals of the CH_3 and CH_3O groups at C(2) of the main products, which are epimers at C(4) (1.15:1=**22**(4*S*)/**22**(4*R*)) in the crude reaction mixture: **22**(4*S*): ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.35 (s, 3H, CH_3(2)), 3.41 (s, 3H, CH_3O); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 20.7 (CH_3(2)), 49.7 (CH_3O); **22**(4*R*): ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.48 (s, 3H, CH_3(2)), 3.22 (s, 3H, CH_3O); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 22.7 (CH_3(2)), 49.4 (CH_3O).

4.19. (2*S*/2*R*,4*S*/4*R*,7*R*,1′*R*,2′*R*,3a′*S*,4′*S*,7a′*R*)-7-Allyl-2-hydroxy-2-methyl-4-(1′-hydroxy-2′-methyl-2′,3′,3a′,4′,7′,7a′-hexahydro-1*H*-inden-4′-yl)-3,4,7,8-tetrahydro-2*H*,5*H*-pyrano[4,3-*b*]pyran-5-one (23) and (6*R*,1′*S*/1′*R*,1″*R*,2″*R*,3a″*S*,4″*S*,7a″*R*)-6-allyl-4-hydroxy-3-[3′-oxo-1′-(1″-hydroxy-2″-methyl-2″,3″,3a″,4″,7″,7a″-hexahydro-1*H*-inden-4″-yl)but-1′-yl]-5,6-dihydro-2*H*-pyran-2-one (24)

The crude ketal product from the previous reaction (ca. 80 mg) was dissolved in a mixture of THF (6 mL), water (4 mL) and concd HCl (0.4 mL) and stirred rapidly for 1.5 h at room temperature. The solution was then quenched with satd aq $NaHCO_3$ (10 mL) and extracted with ethyl acetate (4×15 mL). The combined organic layers were dried over $MgSO_4$ and evaporated to dryness. The product mixture was separated by flash chromatography on silica gel (petroleum ether/ethyl acetate, 2:1). Three products were generally isolated from the column. The first, less stable product remains unidentified. Products **23** and **24**, epimers at C(4), in an approximate 1:1 ratio, were isolated in ca. 20% each (over three steps). Compound **23** (15 mg, 0.04 mmol, 20%), a colourless oil, is a mixture of two anomeric hemiketals (∼2.5:1=2*R*/2*S*). $[\alpha]_D^{20}$ +31.2 (*c* 0.475, acetone). IR (cm^{-1}) 3400 (br), 2925, 2854, 1682, 1634; ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 0.98 (d, 3H, CH_3(2′), $J_{CH_3,2'}$ = 7.1), 1.14 (dtd, 1H, H(3′*endo*), $J_{3',3'}$=12.7, $J_{3',2}$∼$J_{3',3a'}$∼10.3, $J_{3',lr}$∼2–3), 1.48 (dd, 1H, H(3*ax*), $J_{3,3}$=14.0, $J_{3,4}$=12.7), 1.56 (s, 3H, CH_3(2)); minor diastereomer (2*S*): 1.41 (s, 3H, CH_3(2)), 1.68 (m, 2H, H(3a′)), OH, $J_{3a',3'}$= 10.3, $J_{3a',3'}$∼$J_{3a',7a'}$∼7.8, $J_{3a',4'}$∼3), 1.88 (m, 1H, H(3′*exo*)), 1.95 (m, 1H, H(7′)), 1.96 (dd, 1H, H(3*eq*) $J_{3,3}$=14.0, $J_{3,4}$=6.3), 2.02 (m, 1H, H(2′)), 2.04 (m, 1H, H(7a′)), 2.07 (m, 1H, H(7′)), 2.29 (m, 1H, H(8), $J_{8,8}$=17.5, $J_{8,7}$∼3.3, $J_{8,lr}$∼0.5), 2.42 (m, 1H, H(8), $J_{8,8}$=17.5, $J_{8,7}$∼12.7, $J_{8,4}$= 3.1), 2.46 (m, 1H, H(1″)), 2.56 (m, 1H, H(1″), $J_{1'',1''}$= 14.15, $J_{1'',7}$∼6.8, $J_{1'',2''}$∼5.8, $J_{1'',3''}$∼$J_{1'',3''}$∼1), 2.90 (m, 1H, H(4), $J_{4,3}$∼12.7, $J_{4,3}$∼6.3, $J_{4,4'}$∼3, $J_{4,8}$∼3); minor diastereomer (2*S*): 2.80 (m, 1H, H (4)), 3.07 (m, 1H, H(4′), $w_{1/2}$= 9.5); minor diastereomer (2*S*): 2.97 (m, 1H, H(4′)), 4.08 (dt, 1H, H(1′), J=7.4, J∼$J_{1',OH}$∼5.0), 4.36 (m, 1H, H(7), $J_{7,8}$=12.7, $J_{7,1''}$=7.5, $J_{7,1''}$=5.1, $J_{7,8}$=2.9), 5.17 (m, 2H, H(3″)), 5.62 (m, 1H, H(5′), $J_{5',6'}$=10.1), 5.83 (m,1H, H(2″), $J_{2'',3''trans}$=17.2, $J_{2'',3''cis}$=10.1, $J_{2'',1''}$∼$J_{2'',1''}$∼7.0), 5.87 (m, 1H, H(6′), $J_{6',5'}$=10.1). ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) 15.6, 21.6, 28.4 (CH_3(2)), 31.9 (C(4)), 33.2, 33.7, 34.5, 36.4, 37.6 (C(4′)), 38.7, 40.7, 40.8, 73.8, 77.8, 98.7 (C(2)), 103.7, 118.9, 126.5, 130.4, 132.2, 164.3, 166.3; minor diastereomer (2*S*): 24.3 (CH_3(2)), 35.2 (C(4)), 38.3 (C(4′)), 101.5 (C(2)); MS (EI, 70 eV, 130 °C): 374 (9, M^+), 356 (13, M^+-H_2O), 223 (40.5, M^+−hydrindene unit), 202 (25), 181 (45.5), 163 (29), 159 (53), 144 (67.5), 95 (91), 91 (100); HRMS (EI, 70 eV, 130 °C) calcd for $C_{22}H_{30}O_5$: 374.2093, found: 374.2100. NOE crosspeaks 4′/3′*endo*, 3′*endo*/CH_3(2′) establish configuration at C(4′); 3*eq*/5′, 4/5′ as well as the large coupling constant 4/3*ax* confirm the configuration at C(4); configuration of the anomeric centre C(2) of the two anomers was determined by comparison. Whereas the minor compound shows a strong NOE crosspeak CH_3(2)/4, no such effect is observed with the main compound.

Compound **24** (15 mg, 0.04 mmol, 20%) is a colourless oil, which exists mainly as ketone. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 0.97 (d, 3H, CH_3(2″), $J_{CH_3,2''}$ = 7.0), 1.08 (m, 1H, H(3″), $J_{3'',3''}$=12.6, $J_{3'',3a''}$∼$J_{3'',2''}$∼11.4), 1.77 (dt, 1H, H(3″), $J_{3'',3''}$=12.6, $J_{3'',3a''}$∼$J_{3'',2''}$∼7.2), 1.90 (m, 1H, H(3a″)), 1.94 (m, 1H, H(2″)), 2.07 (m, 2H, H(7″,7″)), 2.16 (s, 3H, $COCH_3$), 2.30 (tt, 1H, H(7″a), J=J=8.0, J=J=5.6), 2.41 (dd, 1H, H(5), $J_{5,5}$=17.8, $J_{5,6}$∼3.6), 2.44 (m, 1H, H(1‴), $J_{1''',1'''}$=14.4, $J_{1''',2'''}$∼$J_{1''',6}$∼6.8), 2.46 (dd, 1H, H(5), $J_{5,5}$=17.8, $J_{5,6}$=12.8), 2.52 (m, 1H, H(1‴), $J_{1''',1'''}$=14.4, $J_{1''',2'''}$=6.8, $J_{1''',6}$=5.6), 2.61 (m, 1H, H(4″), $J_{4'',1'}$∼10.5, $J_{4'',5''}$=5.1), 2.80 (td, 1H, H(1′), $J_{1',2'}$∼$J_{1',4''}$∼10.5, $J_{1',2'}$=1.6), 2.82 (dd, 1H, H(2′), $J_{2',2'}$=19.8, $J_{2',1'}$=1.6), 3.39 (dd, 1H, H(2′), $J_{2',2'}$=19.8, $J_{2',1'}$=10.6), 3.96 (dd, 1H, H(1″), $J_{1'',2''}$∼$J_{1'',7''a}$∼6.2), 4.32 (m, 1H, H(6), $J_{6,5}$=12.8, $J_{6,5}$=3.6, $J_{6,1'''}$=5.6, $J_{6,1'''}$=6.7), 5.14–5.20 (m,

2H, H(3‴,3‴), $J_{3‴,2‴}$=16.4, $J_{3‴,2‴}$=10.9), 5.83 (ddt, 1H, H(2‴), $J_{2‴,3‴}$=16.5, $J_{2‴,3‴}$=10.7, $J_{2‴1‴}$∼$J_{2‴1‴}$∼7.1), 5.88 (dd,1H, H(5″), $J_{5″,6″}$=9.85, $J_{5″,4″}$=5.06), 5.93 (dt, 1H, H(6″), $J_{6″,5″}$=9.85, $J_{6″,7″}$=$J_{6″,7″}$=4.04), 9.23 (br s, OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 15.3, 22.3, 31.4, 34.0, 35.3, 38.4, 38.5, 38.7, 38.75, 39.1, 39.9, 46.6, 74.5, 78.7, 106.5, 119.3, 129.8, 130.7, 132.55, 167.4, 167.6, 214.9; MS (EI, 70 eV, 140 °C): 374 (9, M^+), 356 (18, M^+-H_2O), 316 (22, $M^+-(CH_3)_2CO$), 317 (22.5), 223 (35.5, M^+−hydrindene unit), 220 (33), 172 (44), 163 (35), 149 (42), 137 (39), 133 (41), 131 (50), 91 (100).

4.20. 8-Methylene-2-oxabicyclo[2.2.2]octane-3,5-dione (25)

(*R*)-6-Allyldihydropyran-2,4-dione **4** (50 mg, 0.32 mmol) was dissolved in degassed acetic acid (5.5 mL). $3Mn(OAc)_3\cdot 7H_2O$ (259 mg, 0.96 mmol) and $Cu(OAc)_2\cdot H_2O$ (97 mg, 0.49 mmol) were added, and the solution was stirred at 35 °C for 2.5 h. It was then diluted with ethyl acetate (30 mL) and washed with satd aq $NaHCO_3$ (4×15 mL). The solvent was removed under reduced pressure, and the product was obtained by crystallization from dichloromethane/pentane (47%). Mp=171–172 °C (possibly by conversion to 2-hydroxy-6-methylbenzoic acid (mp 171 °C) via thermal retro Diels–Alder reaction). $[\alpha]_D^{20}$ +12.9 (*c* 0.38, acetone). IR (cm^{-1}) 2974, 2330, 1767, 1738, 1733, 1699, 1683, 1657, 1652, 1606. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 2.42 (dd, 1H, H(6), $J_{6,6}$=19.2, $J_{6,1}$∼1.52), 2.58 (dq, 1H, H(7), $J_{7,7}$=17.43, $J_{7,1'}$∼$J_{7,1'}$∼$J_{7,1}$∼1.77), 2.76 (dt, 1H, H(6), $J_{6,6}$=19.2, $J_{6,1}$∼$J_{6,7}$∼3.28), 2.95 (m, 1H, H(7), $J_{7,7}$=17.43, $J_{7,1}$∼3.8, $J_{7,6}$∼3.3, $J_{7,1'}$∼$J_{7,1'}$∼2.78), 4.05 (s, 1H, H(4)), 5.07 (m, 1H, H(1), $J_{1,7}$∼$J_{1,6}$∼3.8, $J_{1,7}$∼$J_{1,6}$∼1.8–1.5), 5.12 (m, 1H, H(1′), $J_{1',1'}$∼2.28, $J_{1',\ 7}$∼2.02), 5.23 (m, 1H, H(1′), $J_{1',1'}$∼2.28, $J_{1',7}$∼2.52, $J_{1',7}$<1.5); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 33.45, 41.6, 67.6, 73.6, 116.7, 131.4, 166.6, 197.3; MS (EI, 70 eV, 30 °C) 152 (18, M^+), 134 (8, M^+-H_2O), 110 (53, M^+-CH_2CO), 108 (42, M^+-CO_2), 82 (100), 54 (82). Anal. Calcd for $C_8H_8O_3$: C=63.15%, H=5.30; found: C=63.15%, H=5.52%.

4.21. (2*R*,3*R*,3a*R*,5a*S*,7*S*,13*R*,13a*S*,13b*S*)-10-Allyl-2,7-dimethyl-1,2,3,3a,5a,9,10,13,13a,13b-decahydro-7,13-methano-12*H*-pyrano[3,4-*d*]indeno[4,5-*g*]-1,3-oxacin-3-ol (26) and (2*R*,3*R*,3a*R*,5a*S*,7*S*,13*R*,13a*S*,13b*S*)-2,7,12-trimethyl-1,2,3,3a,5a,13,13a,13b-octahydro-7,13-methanobenzo[*d*]indeno[4,5-*g*]-1,3-dioxacin-3-ol (27)

Compound **24** (38 mg, 98 μmol), $3Mn(OAc)_3\cdot 7H_2O$ (79 mg, 0.29 mmol) and $Cu(OAc)_2\cdot H_2O$ (29 mg, 0.15 mmol) were stirred in degassed acetic acid (2 mL) at 35 °C for 2.5 h. The solution was then diluted with ethyl acetate, washed with satd aq $NaHCO_3$ and dried over $MgSO_4$. The products were separated by flash chromatography on silica gel (petroleum ether/ethyl acetate 2:1). From these products the two main compounds **26** (7.3 mg, 20 μmol, 20%) and **27** (5.5 mg, 17 μmol, 17%) could be isolated and characterized as a colourless oil. Compound **27**: $[\alpha]_D^{20}$ +25,0 (*c* 0.12, acetone). IR (cm^{-1}, film) 3503 (br), 3030, 2876, 1584, 1264. ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 1.11 (d, 3H, CH_3(2), $J_{CH_{3,2}}$ = 6.9), 1.34 (td, 1H, H(1*endo*), $J_{1,1}$=12.4, $J_{1,2}$=12.1, $J_{1,13b}$=5.8), 1.53 (dt, 1H, H(13a), $J_{13a,13b}$=12.5, $J_{13a,5a}$=3.1, $J_{13a,13}$=2.9), ∼1.5 (br, 1H, OH(3)), 1.56 (s, 3H, CH_3(7)), 1.62 (ddd, 1H, H(14*endo*), $J_{14,14}$=12.8, $J_{14,13}$=3.0, $J_{14,13b}$=0.6), 2.05 (m, 1H, H(2), $J_{2,1}$=12.1, $J_{2,1}$=8.4, J_{2,CH_3}=6.8, $J_{2,3}$=3.4), 2.29 (dd, 1H, H(14*exo*), $J_{14,14}$=12.8, $J_{14,13}$=2.8), 2.30 (s, 3H, CH_3(12)), 2.35 (dt, 1H, H(1), $J_{1,1}$=12.4, $J_{1,2}$=$J_{1,13b}$=8.4), 2.52 (m, 1H, H(13b), $J_{13b,13a}$=12.5, $J_{13b,3a}$=8.8, $J_{13b,1}$=8.4, 5.8), 2.67 (m, 1H, H(3a), $J_{3a,13b}$=8.8, $J_{3a,4}$=3.7, $J_{3a,3}$=3.3, $J_{3a,5}$=2.6), 3.17 (ddd, 1H, H(13), $J_{13,14}$=3.0, 2.8, $J_{13,13a}$=2.9), 3.97 (dd, 1H, H(3), $J_{3,2}$=3.4, $J_{3,3a}$=3.3), 4.02 (dd, 1H, H(5a), $J_{5a,5}$=5.8, $J_{5a,13a}$=3.1), 6.00 (dd, 1H, H(4), $J_{4,5}$=9.7, $J_{4,3a}$=3.7), 6.05 (ddd, 1H, H(5), $J_{5,4}$=9.7, $J_{5,5a}$=5.8, $J_{5,3a}$=2.6), 6.74 (d, 2H, H(9,11), $J_{9,10}$=$J_{11,10}$=7.9), 7.04 (t, 1H, H(10), $J_{10,9}$=$J_{10,11}$=7.8); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) 14.3, 18.45, 27.8, 28.3, 28.8, 31.8, 37.7, 39.05, 42.1, 47.1, 63.7, 77.1, 97.7, 113.1, 122.2, 124.8, 127.2, 129.6, 130.45, 135.6, 155.6; MS (EI, 70 eV, 110 °C): *m*/*z* (%)=326 (77, M^+); 308 (11, M^+-H_2O); 269 (93, $M-CH_2COCH_3$), 250 (26), 235 (35), 177 (39), 159 (70), 91 (100); HRMS (EI, 70 eV, 110 °C) calcd for $C_{21}H_{26}O_3$: 326.1882, found: 326.1877. Significant NOESY crosspeaks: 13a/5a establishes the vicinal cis position, 1*endo*/CH_3(2) and 1*endo*/13a as well as OH/13a and OH/4 (visible in C_6D_6) confirm the *endo* position of 13a and 5a, 14*exo*/13b as well as the *w*-coupling 14*endo*/13a establish the *R*-configuration of C(13).

Compound **26**: $[\alpha]_D^{20}$ +18.0 (*c* 0.205, acetone). IR (cm^{-1}, film) 3502 (br), 2929, 1704, 1645. ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 1.10 (d, 3H, CH_3(2), $J_{CH_{3,2}}$ = 6.8), 1.43 (m, 1H, H(1*endo*), $J_{1,1}$=$J_{1,2}$=12.4, $J_{1,13b}$=6.0), 1.51 (s, 3H, CH_3(7)), 1.52 (m, 1H, H(14*endo*), $J_{14,14}$=13.3, $J_{14,13a}$=3.0, $J_{14,13b}$=0.6), 1.615 (m, 1H, H(13a), $J_{13a,13b}$=12.5, $J_{13a,5a}$=3.4, $J_{13a,13}$=2.9), 2.01 (m, 1H, H(2), $J_{2,1}$=12.4, $J_{2,1}$=8.9, J_{2,CH_3} = 6.8, $J_{2,3}$=3.4), 2.219 (dd, 1H, H(14*exo*), $J_{14,14}$=13.3, $J_{14,13}$=2.6), 2.22 (ddd, 1H, H(1*exo*), $J_{1,1}$=12.4, $J_{1,2}$=8.9, $J_{1,13b}$=7.8), 2.32 (ddd, 1H, H(9*exo*), $J_{9,9}$=17.1, $J_{9,10}$=4.0, *J*=1.1), 2.35 (m, 1H, H(13b), $J_{13b,13a}$=12.5, $J_{13b,3a}$=8.8, $J_{13b,1}$=7.8, $J_{13b,1}$=6.0), 2.46 (m, 1H, H(1′), $J_{1',1'}$∼14.2, $J_{1',2'}$=$J_{1',10}$=7.1, $J_{1',3'}$∼$J_{1',3'}$=1), 2.55 (m, 1H, H(1′), $J_{1',1'}$=14.2, $J_{1',2'}$∼6.8–7, $J_{1',10}$=5.6, $J_{1',3'}$∼$J_{1',3'}$∼1.3), 2.64 (dd, 1H, H(9*endo*), $J_{9,9}$=17.1, $J_{9,10}$=12.1), 2.62 (m, 1H, H(3a), $J_{3a.13b}$=8.8, $J_{3a,4}$=3.8, $J_{3a,3}$=3.3, $J_{3a,5}$=2.6), 2.90 (m, 1H, H(13), $J_{13,14}$=3.0, $J_{13,13a}$=2.9, $J_{13,14}$=2.6), 3.97 (dd, 1H, H(3), $J_{3,2}$=3.4, $J_{3,3a}$=3.3), 3.98 (dd, 1H, H(5a), $J_{5a,5}$=5.6, $J_{5a,13a}$=3.4), 4.48 (m, 1H, H(10), $J_{10,9}$=12.1, $J_{10,1'}$=7.4, $J_{10,9}$=4.0, $J_{10,1'}$=5.4), 5.162 (m, 1H, H(3′), $J_{3',3'}$=2.0, $J_{3',2'}$=9.9, $J_{3',1'}$∼$J_{3',1'}$∼1.0), 5.167 (m, 1H, H(3′), $J_{3',3'}$=2.0, $J_{3',2'}$=17.5, $J_{3',1'}$∼$J_{3',1'}$∼1.3), 5.82 (ddt, 1H, H(2′), $J_{2',3'}$=17.5, $J_{2',3'}$=9.9, $J_{2',1'}$=$J_{2',1'}$=6.8), 6.01 (m, 1H, H(5), $J_{5,4}$=10.0, $J_{5,5a}$=5.6, $J_{5,3a}$=2.6), 6.07 (dd, 1H, H(4), $J_{4,5}$=10.0 $J_{4,3a}$=3.8); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) 14.05, 26.4, 27.2, 28.85, 30.9, 31.9, 37.4, 39.0, 39.3, 41.0, 47.1, 65.0, 74.7, 77.3, 100.5, 104.2, 119.0, 127.8, 131.7, 132.1, 165.9, 166.6; MS (EI, 70 eV, 130 °C): *m*/*z* (%)=372 (30, M^+), 301 (75, $M^+-C_4H_6OH$), 223 (26), 181 (37.5), 163 (23), 155 (44), 91 (100); HRMS (EI, 70 eV, 130 °C) calcd for $C_{22}H_{26}O_5$: 372.1937, found: 372.1928. Significant NOESY crosspeaks: 13a/5a establishes the vicinal cis position, 1*endo*/CH_3(2) and 1*endo*/13a as well as OH/13a and OH/5a (visible in C_6D_6) confirm the *endo* position of 13a and 5a, 14*exo*/13b as well as the *w*-coupling 14*endo*/13a establish the *R*-configuration of C(13).

4.22. (2*R*,3*R*,3a*R*,5a*S*,7*S*,13*R*,13a*S*,13b*S*)-3-Acetoxy-10-allyl-2,7-dimethyl-1,2,3,3a,5a,9,10,13,13a,13b-decahydro-7,13-methano-12*H*-pyrano[3,4-*d*]indeno[4,5-*g*]-1,3-oxacin (28)

Compound **26** (7.3 mg, 19.3 μmol) and DMAP (40 mg, 328 μmol) were dissolved in dichloromethane and cooled to 0 °C. Acetic anhydride (0.6 mL) was added and the solution was allowed to slowly warm to room temperature and stirred overnight. Water was added and the mixture was extracted with diethyl ether (4×). The combined organic layers were washed with 3% aq HCl, satd aq $NaHCO_3$ and brine, and dried over $MgSO_4$. The solvent was removed by rotary evaporation and the residue purified by flash chromatography on silica gel (hexane/ethyl acetate 3:1) yielding **28** (4.1 mg, 10 μmol, 52%). $[\alpha]_D^{20}$ +10.5 (*c* 0.2, acetone). IR (cm^{-1}, film) 2925, 1735, 1707, 1647, 1401; ^1H NMR (600 MHz, $CDCl_3$) δ (ppm) 1.00 (d, 3H, $CH_3(2)$, $J_{CH_{3,2}} = 6.7$), 1.43 (m, 1H, H(1*endo*), $J_{1,1}$=$J_{1,2}$=12.4, $J_{1,13b}$=6.1), 1.505 (s, 3H, $CH_3(7)$), 1.54 (m, 1H, H(14*endo*) $J_{14,14}$=13.4, $J_{14,13a}$=3.55, $J_{14,13b}$=0.6), 1.57 (m, 1H, H(13a), $J_{13a,13b}$=12.0, $J_{13a,5a}$~$J_{13a,13}$~3.0), 1.94 (s, 3H, $COCH_3$), 2.14 (m, 1H, H(2)), 2.22 (dd, 1H, H(14*exo*), $J_{14,14}$=13.3, $J_{14,13}$~2.8), 2.27 (dt, 1H, H(1*exo*), $J_{1,1}$=12.4, $J_{1,2}$~$J_{1,13b}$~8.7), 2.33 (ddd, 1H, H(9*exo*), $J_{9,9}$= 17.3, $J_{9,10}$=3.9, J=1.1), 2.40 (m, 1H, H(13b), $J_{13b,13a}$= 12.5, $J_{13b,3a}$~$J_{13b,1}$~9.3, $J_{13b,1}$=6.1), 2.465 (m, 1H, H(1′), $J_{1',1'}$~14.2, $J_{1',2'}$=$J_{1',10}$=7.2, $J_{1',3'}$~$J_{1',3'}$~1.3), 2.585 (m, 1H, H(1′), $J_{1',1'}$=14.2, $J_{1',2'}$=6.9, $J_{1',10}$=5.7, $J_{1',3'}$~$J_{1',3'}$~ 1.5), 2.64 (dd, 1H, H(9), $J_{9,9}$=17.3, $J_{9,10}$=12.2), 2.73 (m, 1H, H(3a), $J_{3a.13b}$=9.6, $J_{3a,4}$~$J_{3a,3}$~$J_{3a,5}$~2.7), 2.89 (m, 1H, H(13), $J_{13,14}$~$J_{13,13a}$~$J_{13,14}$~2.4), 3.94 (dd, 1H, H(5a), $J_{5a,5}$=5.7, $J_{5a,13a}$=3.8), 4.485 (m, 1H, H(10), $J_{10,9}$=12.3, $J_{10,1'}$=6.6, $J_{10,1'}$=5.8, $J_{10,9}$=3.8), 5.15–5.20 (m, 2H, H(3′)), 5.255 (dd, 1H, H(3), $J_{3,2}$~$J_{3,3a}$~3.7), 5.84 (m, 1H, H(2′)), 5.86 (m, 1H, H(5)), 5.97 (dd, 1H, H(4), $J_{4,5}$= 10.0, $J_{4,3a}$=3.9); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 14.2, 21.1, 26.4, 27.2, 28.9, 31.2, 31.9, 37.6, 38.2, 39.1, 40.4, 46.0, 64.9, 74.9, 79.4, 100.5, 104.1, 119.0, 126.3, 131.4, 132.2, 165.9, 166.85, 170.9; MS (EI, 70 eV, 100 °C): *m*/*z* (%)=414 (18.5, M^+), 284 (24), 256 (89), 213 (15); HRMS (EI, 70 eV, 100 °C) calcd for $C_{24}H_{30}O_6$: 414.2042, found: 414.205. Significant NOESY crosspeaks: 13a/5a establishes the vicinal cis position, 1*endo*/$CH_3(2)$ and 1*endo*/13a as well as 13a/CH_3COO confirm the *endo* position of 13a and 5a, 14*exo*/13b as well as the *w*-coupling 14*endo*/13a establish the *R*-configuration of C(13).

4.23. (2*R*,3*R*,3a*R*,5a*S*,7*S*,13*R*,13a*S*,13b*S*)-3-Acetoxy-2,7,12-trimethyl-1,2,3,3a,5a,13,13a,13b-octahydro-7,13-methanobenzo[*d*]indeno[4,5-*g*]-1,3-dioxacin (29)

Compound **27** (3.3 mg, 10 μmol) and DMAP (20 mg, 165 μmol) were dissolved in dichloromethane and cooled to 0 °C. Acetic anhydride (0.3 mL) was added and the solution was allowed to slowly warm to room temperature and stirred overnight. Then water was added and the mixture was extracted with diethyl ether (4×). The combined organic layers were washed with 3% aq HCl, satd aq $NaHCO_3$ and brine, and dried over $MgSO_4$. The solvent was removed by rotary evaporation and the residue purified by flash chromatography (hexane/ethyl acetate 4:1) yielding **29** (2.3 mg, 6.25 μmol, 62.5%). $[\alpha]_D^{20}$ +30.90 (*c* 0.055, acetone). IR (cm^{-1}, film) 2926, 1740, 1466; ^1H NMR (600 MHz, $CDCl_3$) δ (ppm) 1.01 (d, 3H, $CH_3(2)$, $J_{CH_{3,2}} = 6.7$), 1.30 (m, 1H, H(1)), 1.42 (dt, 1H, H(13a), $J_{13a,13b}$=12.5, $J_{13a,5a}$~ $J_{13a,13}$~3.0), 1.56 (s, 3H, C(7)CH_3), 1.625 (ddd, 1H, H(14), $J_{14,14}$=13.3, $J_{14,13}$=3.5, $J_{14,13b}$=0.7), 1.88 (s, 3H, $COCH_3$), 2.205 (m, 1H, H(2)), 2.29 (dd, 1H, H(14), $J_{14,14}$=13.3, $J_{14,13}$=2.9), 2.32 (s, 3H, $CH_3(12)$), 2.42 (dt, 1H, H(1), $J_{1,1}$=12.8, $J_{1,2}$=$J_{1,13b}$=8.5), 2.59 (m, 1H, H(13b), $J_{13b,13a}$= 12.5, $J_{13b,3a}$~$J_{13b,1}$~9.1, $J_{13b,1}$=6.2), 2.77 (m, 1H, H(3a), $J_{3a,13b}$=9.7, $J_{3a,4}$~$J_{3a,3}$~$J_{3a,5}$~3.2), 3.18 (td, 1H, H(13), $J_{13,14}$=$J_{13,13a}$=3.0, $J_{13,14}$=2.7), 3.99 (dd, 1H, H(5a), $J_{5a,5}$=6.0, $J_{5a,13a}$=3.5), 5.29 (t, 1H, H(3), $J_{3,2}$~$J_{3,3a}$~3.7), 5.86 (ddd, 1H, H(5), $J_{5,4}$=10.1, $J_{5,5a}$=5.8, $J_{5,3a}$=2.5), 5.91 (dd, 1H, H(4), $J_{4,5}$=10.1, $J_{4,3a}$=3.7), 6.76 (m, 1H, H(9), $J_{9,10}$=7.9), 6.77 (m, 1H, H(11), $J_{11,10}$=7.9), 7.07 (t, 1H, H(10), $J_{10,9}$=$J_{10,11}$=7.9); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) 14.4, 18.1, 21.0, 28.55, 29.0, 32.05, 38.1, 41.85, 46.0, 63.8, 79.5, 97.7, 113.2,122.2, 124.9, 127.2, 127.3, 130.5, 135.4, 155.8, 170.55; MS (EI, 70 eV, 130 °C): *m*/*z* (%)=369 (14, $M+H^+$), 368 (61, M^+), 311 (39), 290 (29.5), 275 (15), 251 (29), 250 (17), 249 (12), 235 (13), 177 (16.5), 159 (44), 157 (19), 149 (20), 132 (25), 131 (31), 97 (34), 91 (41), 85 (30), 84 (51), 83 (91.5), 82 (36), 69 (48), 57 (100), 55 (69); HRMS (EI, 70 eV, 50 °C) calcd for $C_{23}H_{28}O_4$: 368.1988, found: 368.1995. Significant NOESY crosspeaks: 13a/5a establishes the vicinal cis position, 1*endo*/$CH_3(2)$ and 1*endo*/13a confirm the *endo* position of 13a and 5a, 14*exo*/13b as well as the *w*-coupling 14*endo*/13a establish the *R*-configuration of C(13).

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