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Enantioselective Access to Key Intermediates for Salvinorin A and Analogues[‡]

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Access to enantiopure synthetic platforms that can generate key intermediates for salvinorin A analogues through diastereoselective Diels–Alder cycloaddition between an enantiopure sulfinylquinone and semicyclic dienes is described.

Introduction

Among the isolated natural products exhibiting psychodysleptic activities, salvinorin A,[1] which displays strong neurobiological activity (highly specific *kappa* opoid receptor – KOR – ligand) with high medicinal potential and a challenging chemical structure,[2] has emerged as a target of particular interest because of the difficulties involved in modifying the structure of the extracted natural product for SAR studies. Salvinorin A is now recognized as a lead structure for the design of novel opioid receptor-specific ligands.[3] Interestingly, although salvinorin A (**1**) has low affinity for *mu* opoid receptors (MOR),[4] it has been shown to be an allosteric modulator of MOR.[5] To date, structure–activity relationships of **1** have focused on several main areas: i. the 2-position acetoxy group,[6] ii. the 4-position methoxycarbonyl group, iii. the 17-position carbonyl, and iv. the 12-position furan ring.[2,7] Figure 1 summarizes the structure–activity relationships for salvinorin A analogues.

Despite the fact that the nature of the interactions at the C(2) and C(4) positions are well-understood, those at the C(12) position remain unclear. Two salvinorin A···KOR interaction models have been proposed so far.[8] The hydrophobic nature of salvinorin A inherently lends itself to recognition through hydrophobic interactions.[8b] According to the second model,[8a] the furan oxygen may act as a hydrogen-bond acceptor to tyrosine moieties of KOR.

However, both the electron density of the heteroatom acting as a hydrogen-bond acceptor at C(12), and the hydrophobic interactions between the C(12) moiety and KOR are critical to the binding affinity of salvinorin A template analogs to KOR. This hypothesis has been recently

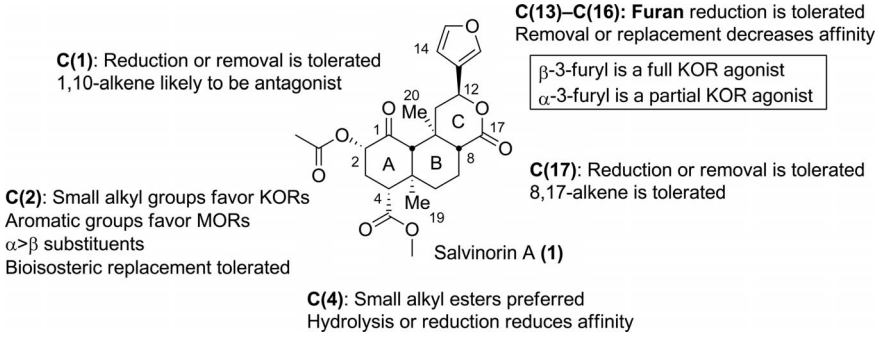

Figure 1. Summary of structure–activity relationships for salvinorin analogues.

supported by the preparation of 12-*epi*-salvinorin A, which exhibits partial agonist properties at KOR with high selectivity.[7] Furthermore, the authors demonstrated that inversion at C(12) has little effect on the position of the furan ring: superimposition with the crystal structure of **1** shows that C(13) and the furan oxygen atom are almost coincident in the two structures. That this subtle change in position

[‡] Total Synthesis of Salvinorin A and Analogues, 1 (Part 1 of a new article series)

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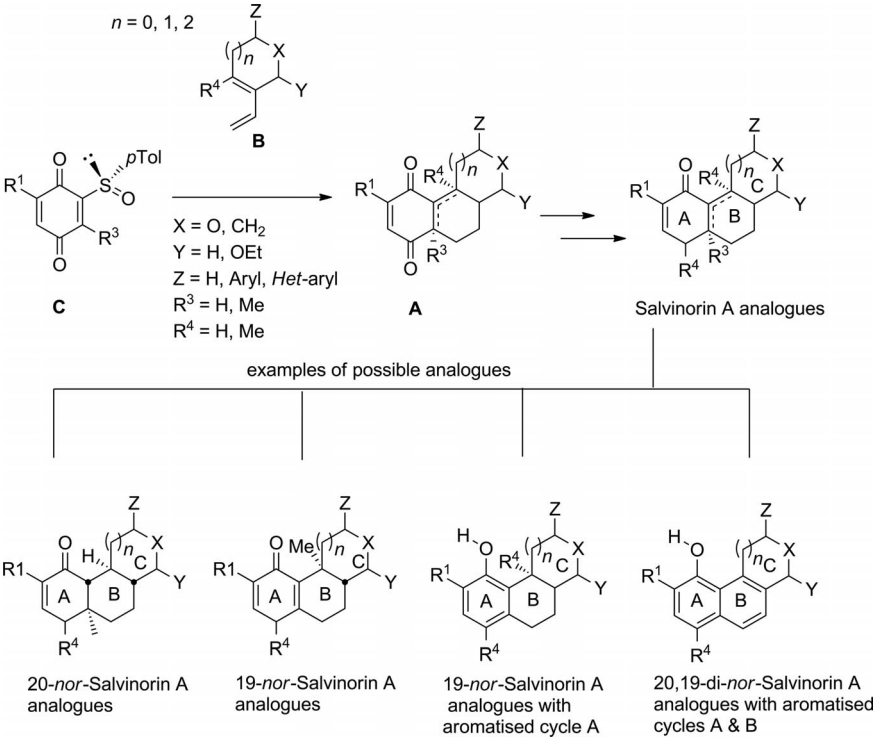


Scheme 1. Diastereoselective Diels–Alder reaction as a key step in the proposed strategy.

and orientation of the furan ring should convert a full agonist into a partial one perhaps represents a key to the mode of action of **1**. Furthermore, no studies have evaluated the importance, if any, of the C(19) and C(20) methyl groups. From their locations on the salvinorin skeleton, modifications to these two quaternary centers are clearly dificult. Finally, the influence of the size of the C-ring has not been investigated. All these parameters should influence the positioning of the furan ring at C(12) within the receptor, which is critical to the binding affinity at KOR.

Four years ago, we embarked on studies towards the total synthesis of salvinorin A through a highly convergent strategy that allows easy modifications at C(2), C(4), and C(12), as well as allowing modifications to both quaternary centers, C-ring size, and relative configuration at C(12).[9]

Two total syntheses of salvinorin A have been reported so far.[10a] One approach, which was developed by Evans and co-workers,[10b] required 29 steps and involved a transannular Michael reaction cascade, whereas the second approach, developed in two phases by Hagiwara's group,[11] required 20[11a] or 15[11b] steps from a Wieland–Miescher ketone.[12]

Our own strategy is based on a highly diastereoselective Diels–Alder cycloaddition of a semicyclic dihydropyran-based diene **B** with an enantiomerically pure sulfinylquinone **C** (Scheme 1). The strength of this strategy is the simultaneous creation of multiple stereogenic centers, and the whole tricyclic skeleton **A** (on a multigram scale) of salvinorin A with the required functional groups for its total synthesis. It also allows a variation of the different important positions for pharmacological purposes (R^1, R^2, X, Y, Z) and allows access to numerous analogues as well as diastereoisomers that are not available by chemical modification of the natural product. This method is also an ideal tool to introduce both angular methyl groups (R^3, R^4), either simultaneously or sequentially, by choosing the appropriate sulfinylquinone and diene precursors, therefore potentially giving access to *nor*-salvinorins or aromatic analogues: cycle A and/or A/B (Scheme 1). Finally, this strategy allows a modification of the size of the C-ring by modification of the dihydropyran skeleton of **B** (five- or seven-membered ring).

In this paper, we report our preliminary results, which demonstrate that the strategy depicted in Scheme 1 (**C**; R^3 = Me and **B**; R^4 = H, Y = H) can be used to open a route to enantiomerically pure synthetic platforms that represent the building blocks of many analogues of salvinorin A. Modifications of the aromatic part at C(12) (i.e., 2-furyl) of the C-ring size (five- or seven-membered rings) and of the quaternary centre at C(5) and/or C(9), should lead to interesting analogues for SAR studies that would give a better understanding of interactions with KOR. We have recently published the preparation of dienes **B** with cyclic *O*,*O*-acetals (X = O, Y = OEt) – as precursors of the C(17) carbonyl group of salvinorin A or hemicetal group of salvinorin J[13] – by ring-closing metathesis of the corresponding 1,7- and 1,8-enynes of propargylic *O*,*O*-acetals.[14] Cycloaddition of these dienes with **C** (R^3 = Me), as well as of dienes **B** with a vinylic methyl group (R^4 = Me) with **C** (R^3 = H) will be disclosed in due course.

Results and Discussion

For initial studies, we selected the model 1,3-diene **3**[15] as a suitable substrate for reaction development with enantiomerically pure sulfinylquinone **2** (Scheme 2). We have already demonstrated that (S_S)-6-methoxy-2-(*p*-tolylsulfinyl)-3-methyl-1,4-benzoquinone (**2**) is a very efficient building block for the construction of functionalized decalins with an angular methyl group, and we have disclosed a new access to Wieland–Miescher diketone analogues.[16] (S_S)-Sulfinylquinone **2** was prepared on large scale within 10 days from methylhydroquione.

By analogy with our previous study,[16] we anticipated that precomplexation of the sulfinylquinone **2** with $ZnBr_2$ would be necessary to obtain good conversion in reasonable time. Thus, by mixing (S_S)-sulfinylquinone **2** with 2 equiv. of $ZnBr_2$ at –20 °C in dichloromethane and adding 2 equiv. of diene **3** after a few minutes, the cycloaddition occurred smoothly and complete conversion was observed after 10 h (Scheme 2).

During our first attempts, we obtained, after work up and purification on demetalated silica gel,[17] very low yields of cycloadduct **4** (15%) and a quantitative amount of thiosulfinate **5**. The quantitative isolation of the latter showed clearly that the cycloaddition occurred completely, because it resulted from the spontaneous desulfinylation reaction of the cycloadduct at room temperature. Finally, we found that rapid filtration at –20 °C of the crude material on standard silica gel, using a mixture of CH_2Cl_2/Et_2O (1:1), delivered the cycloadduct **6** in 95% isolated yield. This first set of experiments, together with a recent paper by the group of Perlmutter[18] describing access to a racemic precursor of 20-*nor*-salvinorin using a similar strategy, confirmed that rapid access to synthetic platforms for the preparation of salvinorin A and analogues as depicted in Scheme 1, was viable.

To demonstrate the versatility of our strategy for the preparation of a range of salvinorin A analogues, we prepared different semicyclic dienes **7a**–**d**, **8a**, **8b**, **9a**, and **9b** using ring-closing enyne metathesis (RCEM) under conditions developed by Mori[19] (Figure 2). Although replacing the furan ring with another heteroaromatic ring results in loss of affinity for KOR,[7,20] the previously unknown diene (±)-**7d** was chosen for its aromatic moiety because it could be derivatized into a quinone and also because it bears the same aromatic substitution pattern as 2,5-dimethoxy-4-methylamphetamine (DOM), which is a serotoninegic psychedelic and 5-HT_2 neuroligand.[21] RCEM reactions leading to dienes **7a**–**d** were performed using Grubbs 1st generation catalyst (1 mol-%), however, these conditions were totally ineffective for the RCEM of the precursors of **8a**, **8b**, **9a**, and **9b**. Finally, seven-membered ring based dienes **8a** and **8b** were obtained in good yields (80 and 70%, respectively),[14] as well as the corresponding five-membered rings **9a** and **9b** (72 and 68%, respectively) by reaction with Grubbs 2nd generation catalyst (5 mol-%) in dichloroethane under an ethylene atmosphere at 80 °C.[22]

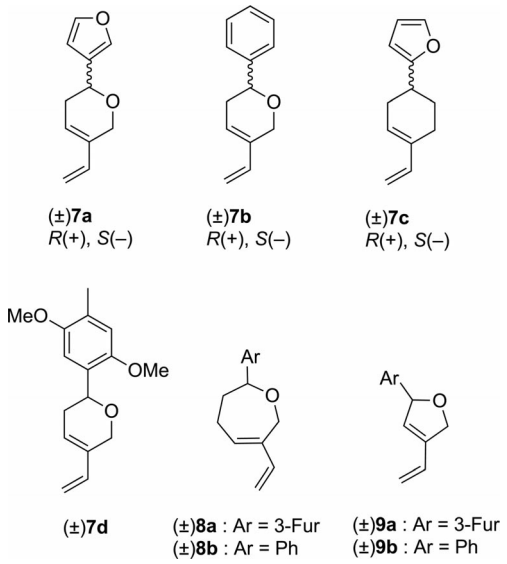
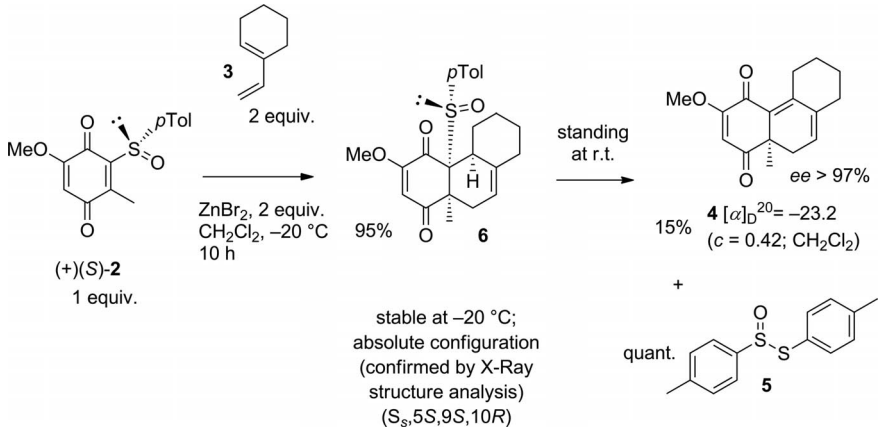


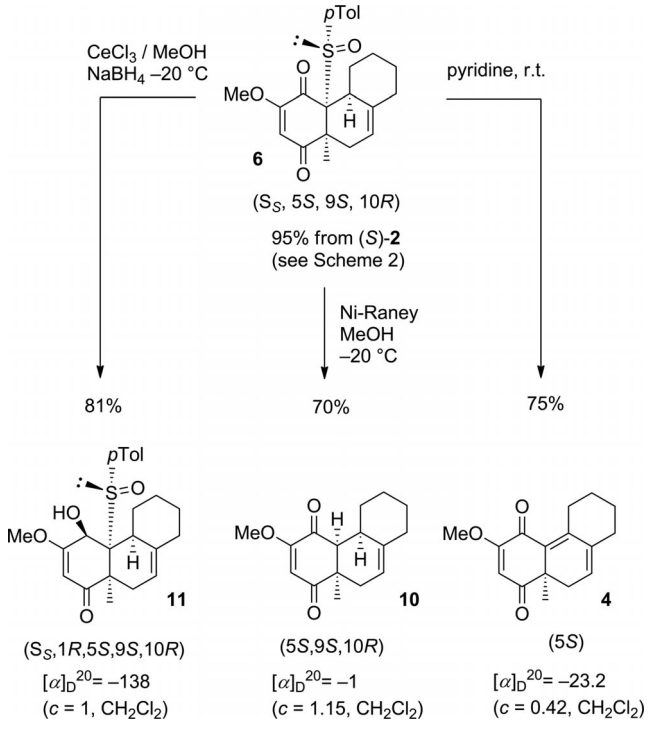
Figure 2. Semicyclic dienes **7**, **8** and **9** prepared as substrates for cycloaddition reactions with dienophile (*S*)-**2**.

Returning to our model reaction (Scheme 2), we observed that cycloadduct **6** was stable at –20 °C for several months (even years) and that it was possible to perform a desulfinylation using Raney-Ni in cold MeOH (–20 °C) to give the corresponding *cis*-decalin **10** in 70% yield. Interest-



Scheme 2. Diels–Alder cycloaddition of sulfinylquinone **2** with model diene **3**.

ingly, applying Luche reduction conditions[23] to cycloadduct **6** stereoselectively afforded alcohol **11** in 81% isolated yield as pure crystals (Scheme 3), showing that the two carbonyl groups at positions C(2) and C(4) can be easily differentiated.



Scheme 3. Desulfinylations and Luche reduction of cycloadduct **6** at –20 °C.

A crystal structure of **11** was obtained that confirmed its relative and absolute configuration (Figure 3) as (S_S,1*R*,5*S*,9*S*,10*R*), which is in agreement with our previously proposed model.[16] The decomposition observed when cycloadduct **6** was warmed to room temperature (Scheme 2) was attributed to a reaction between the sulfenic acid (*p*-TolSOH) – resulting from the *syn*-elimination of the sulfoxide moiety – and the newly formed cycloadduct **4**. Classical sulfenic acid scavengers (Michael acceptors, PPh_3) failed to trap *p*-TolSOH. However, when cycloadduct **6** was warmed (room temp.) in pyridine, compound **4** was obtained in good yield (see Scheme 3).

With these preliminary results in hand, we added racemic dienes **7a**–**d**, **8a** and **9a** (2 equiv.) to (S_S)-sulfinylquinone **2** (1 equiv.) under conditions similar to those described above for **3**. In the case of **7a**–**c**, the resulting cycloadducts **12a**–**c** were isolated with high yields (85–90%). As could be expected from previous work,[24] we observed a kinetic resolution at the benzylic position of the diene during the cycloaddition, which depended on the nature of the substituents. Excess of diene **7** was recovered as an *S*-(–)-enantioenriched mixture, showing that the *R*-(+)-enantiomer of **7** was more reactive; this is in complete agreement with known models (see Scheme 4).

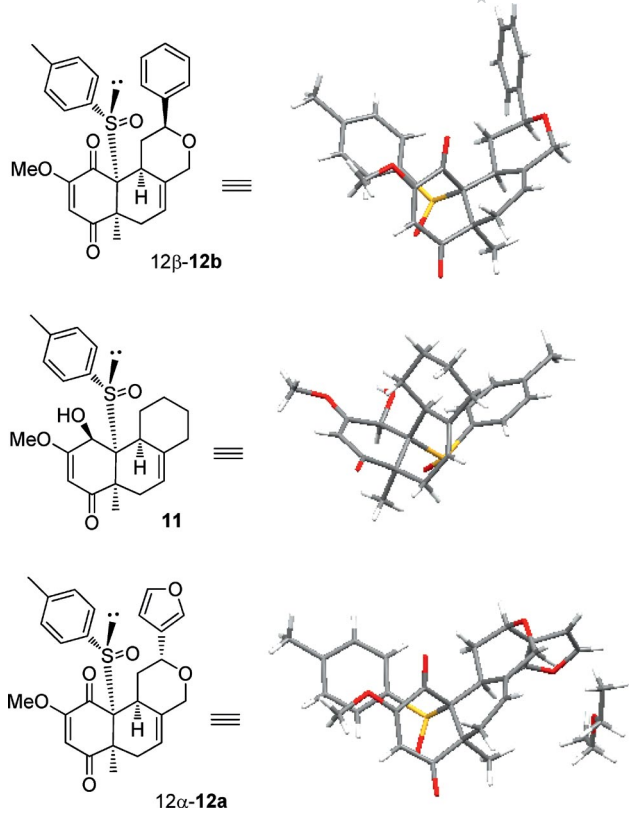


Figure 3. X-ray structures of **11**, 12β-**12b**, and 12α-**12a**.

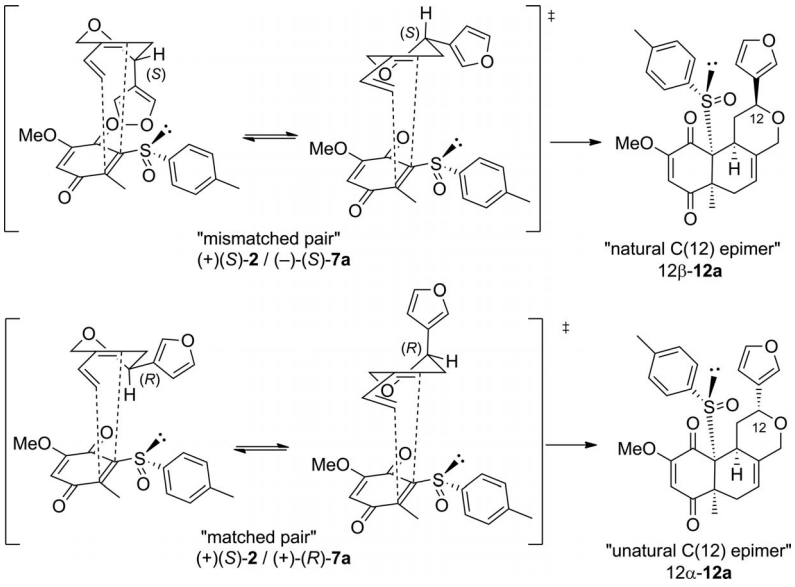
Simple crystallization in cold diethyl ether of a diastereomeric mixture of **12** afforded pure 12α-**12a**–**c**, which were stable at –20 °C, and which were characterized by NMR analysis.

Crystal structures of 12β-**12b** and 12α-**12a** were obtained and their X-ray analyses confirmed their absolute configurations to be (S_S,5*S*,9*S*,10*R*,12*R*) and (S_S,5*S*,9*S*,10*R*,12*S*), respectively (see Figure 3).

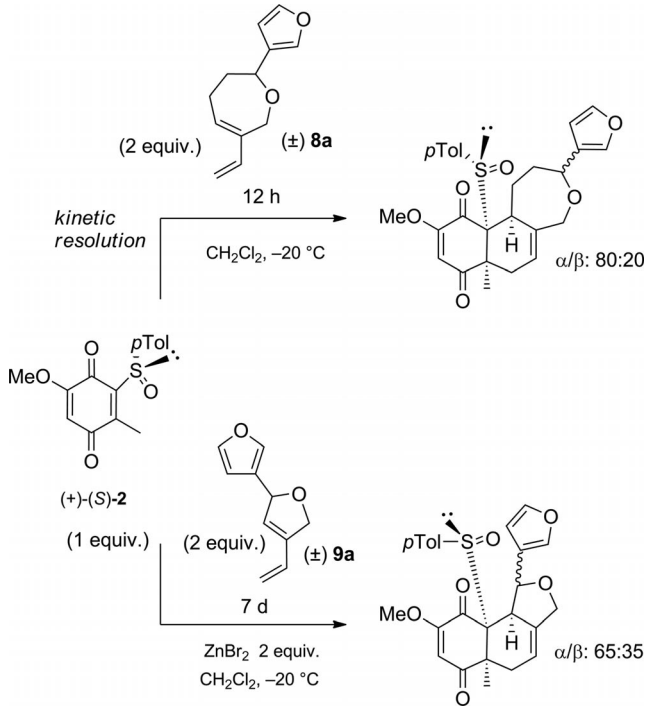
Similar results were observed with dienes **7d**, **8a** and **9a**. The corresponding cycloadducts were obtained in 1 d, 10 h, and 7 d, respectively, with α/β ratios of 95:5, 80:20 and 65:35 (Scheme 5).[25]

Compounds **12a**–**c** were desulfinylated with Raney-Ni at –20 °C, and the resulting *trans*-decalins **13a**–**c** were obtained in 60–67% yields (Scheme 6). In contrast to the cycloadduct **6**, which was desulfinylated with retention of configuration to the *cis*-decalin **10**, a total epimerization at C(10) was observed for cycloadducts **12**, leading to *trans*-decalins **13** during the desulfinylation process. The relative configuration of the decalin skeleton in cycloadducts **13** (*trans*) and **10** (*cis*) was unambiguously assigned by NOESY experiments, and by measuring the coupling constants between protons at C(10) and C(9) (10.2 Hz for **13** and 5 Hz for **10**).

To obtain the required configuration at C(12), we prepared enantiomerically enriched (*S*)-**7a**–**c** and (*R*)-**7a**–**c** using enantioselective enzymatic hydrolysis of the corresponding homoallylic acetate.[26] As the cycloaddition proceeded smoothly within one day with the (*R*)-enantiomers



Scheme 4. Matched and mismatched approaches between enantiomerically pure dienes **7** and (+)-(*S*)-sulfinylquinone **2**.



Scheme 5. Diels–Alder cycloaddition of sulfinylquinone **2** with dienes **8a** and **9a**.

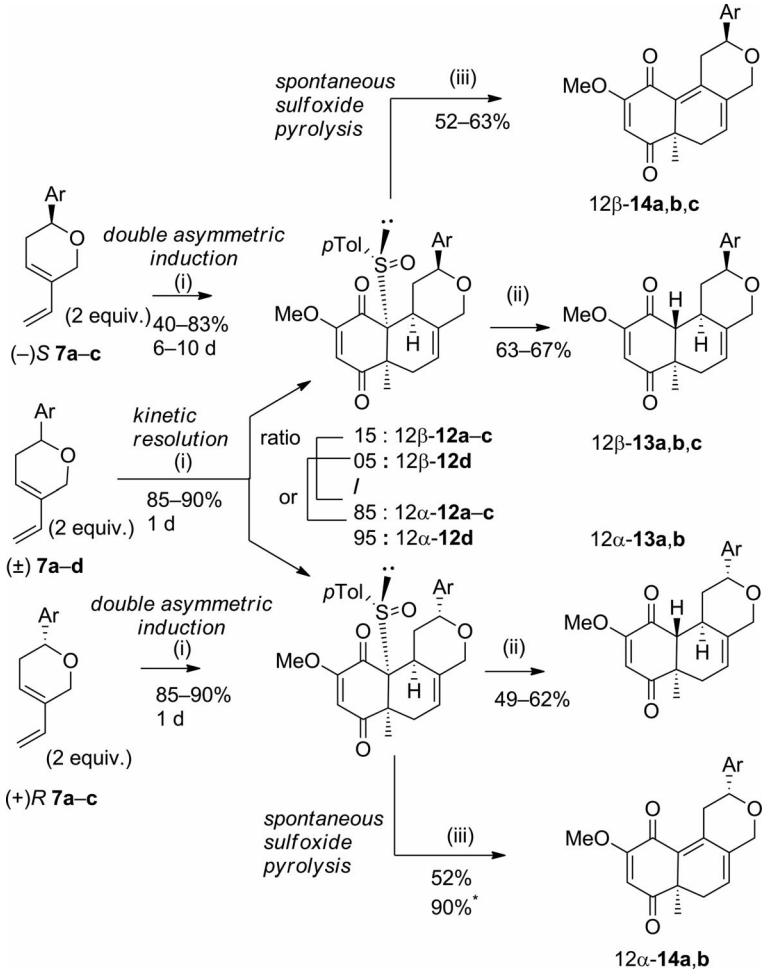
of **7a**–**c** (matched pair), the reaction performed with (*S*)-**7a**–**c** (mismatched pair) was slow (6–10 d), but lead smoothly to the expected enantiopure cycloadducts 12β-**12a**–**c** (Scheme 4 and Scheme 6).[27] In the first case, the cycloadducts 12α-**12a**,**b** ["unnatural C(12) epimers"] were isolated at –20 °C in high yield (>85%) and subsequent desulfinylation using Raney-Ni at –20 °C or standing at room temperature lead to enantiomerically enriched compounds 12α-**13a**,**b** in 49–62% and 12α-**14a**,**b** and 52% yields, respectively (see Scheme 6).

In the second case, the resulting 12β-**12a**–**c** cycloadducts ["natural C(12) epimers"] were much less stable compared to their C(12) epimers, and the crude reaction mixtures were directly treated with Raney-Ni at –20 °C to give desulfinylated compounds (+)-12β-**13a**–**c**[28] in enantiomerically enriched form in 63–67% yield. Conducting an elimination reaction of the same intermediates lead to unsaturated dienones 12β-**14a**–**c** in 52–63% yield. In contrast to their 12α epimers, these 12β dienones were much more stable. Finally, (+)-12β-**13a**,**b** were obtained in 45% and 55% overall yield, which compares favorably with Perlmutter's racemic sequence [32% for (±)12β-**13a**, and 44% for (±)12β-**13b**].[18]

Conclusions

We have reported a short route to enantiomerically pure cycloadducts (+)12β- or (–)12α-**13a**–**c**, with (+)12β-**13a** being a key intermediate in Perlmutter's racemic approach towards 20-*nor*-salvinorin A. The stereoselective cycloaddition of (S_S)-Sulfinylquinone **2** with various semicyclic dienes **7** leads to the controlled formation of four stereogenic centers in one step. This paper describes the first example of a kinetic resolution at the C(12) position.[29] The introduction of a substituent (such as 3-Furyl) at this position is usually stereochemically uncontrolled in diterpenoids synthesis, particularly in the clerodane series.[11,30]

Accessing the dienone (+)12β-**14a** opens a route to salvinorin A, because it represents a useful precursor for the introduction of the C(20) quaternary center after the stereoselective reduction of the C(7)–C(8) double bond. This strategy also opens the way to the synthesis of many analogues of salvinorin A for the evaluation of their KOR selectivity. Accordingly, possible variations in the size of the C-cycle (seven- and five-membered ring) have been assessed



Scheme 6. Preparation of epimeric C(12) compounds (α or β) **12**, **13** and **14**. Reagents and conditions: (i) *S*-(+)-**2** (1 equiv.), $ZnBr_2$ (2 equiv.), CH_2Cl_2, –20 °C; (ii) Raney-Ni, MeOH, –20 °C; (iii) CH_2Cl_2, –20 °C, 5 d or pyridine*, room temp., overnight. * Conversion determined from the ^1H NMR spectra for **14a**, which decomposed on silica gel.

and the transformation of the resulting cycloadducts into salvinorin A analogues will be published in due course.

Experimental Section

General Remarks: Reagents and solvents were purchased as reagent grade and used without further purification. THF was distilled from sodium benzophenone ketyl. Dichloromethane was distilled from CaH_2. $ZnBr_2$ was flamed-dried in the reaction flask under vacuum and under Argon before use. Flash column chromatography (FC) was performed using silica gel 60 for preparative column chromatography (40–63 mm), unless specifically noted otherwise. Demetalled silica gel was prepared according to a published procedure.[17] Thin-layer chromatography (TLC) was performed on glass sheets coated with silica gel 60 F_{254} (otherwise stated), visualization by UV light or through staining with phosphomolybdic acid, $KMnO_4$ or vanillin. Optical rotations were measured with a polarimeter with a sodium lamp and are reported as $[\alpha]_D^{20}$ (*c* is given in g/100 mL, solvent). ^1H and ^{13}C NMR spectra were recorded with a 200, 300, or 400 MHz spectrometer. Chemical shifts are reported in ppm relative to the solvent ($CDCl_3$) resonance δ = 7.26 ppm (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, app s = apparent singlet, m = multiplet, coupling constant in Hz, integration). ^{13}C NMR spectra were also run at various field strengths as indicated; spectra were recorded in $CDCl_3$ using residual undeuterated solvent (δ = 77 ppm) as internal reference. Infra red (IR) spectra were recorded with a diamond ATR spectrometer using neat simples. Infra red frequencies are reported in wavenumbers (cm^{-1}), intensities were determined qualitatively and are reported as strong (s), medium (m), or weak (w). IR measurements were obtained with Universal ATR sampling accessories.

Melting points of solid compounds bearing a sulfoxide were not recorded due to their high instability (even at room temp.).

The following known compounds were isolated as pure samples and showed data matching those of reported compounds: (***S***)-**2**,[16] **3**,[15] (±)-**7b**,[19a] **8a** and **8b**,[14] **9b**.[31]

General Procedure for $ZnBr_2$-Catalyzed Diels–Alder Reactions: To a solution of freshly prepared sulfinylquinone (*S*)-**2** (0.75–1.00 mmol, 1 equiv.) in anhydrous CH_2Cl_2 (10 mL), was added $ZnBr_2$ (2 equiv.) at –78 °C under argon, and the mixture was stirred for 10 min. The appropriate 1,3-diene (2 equiv.) was added and the resulting solution was stored in a fridge at –20 or –40 °C (dry ice/MeCN).

After completion of the reaction, a decoloration of the solution from dark-orange to pale-yellow was observed and the mixture was quenched with cold aqueous NH_4Cl. The cold aqueous phase was extracted with of cold (–20 °C) CH_2Cl_2 (3 × 10 mL). The resulting

organic solution was vacuum filtered through a short pad of silica gel (diameter: 6 cm, height: 3–4 cm) with: i. 150 mL of cold CH_2Cl_2 (–70 °C) to recover optically active diene (enantiopure or enantiomerically enriched if a racemic diene has been used); ii. 200 mL of a 1:1 CH_2Cl_2/Et_2O mixture (–70 °C) to isolate the cycloadduct (Note: some ice crystals may appear if the filtrate is left at –70 °C, which may be filtered).

To avoid spontaneous elimination of the sulfoxide moiety from the cycloadduct, the distillation of solvents must be performed at low temperature (<0 °C). It is possible to obtain white crystals by trituration of the resulting solid in cold Et_2O (–20 °C). When racemic 1,3-diene was used, the diastereomeric purification was performed as follow: the crude diastereomeric mixture (350 mg) was dissolved in cold (–20 °C) Et_2O (50 mL) and placed in the freezer overnight. The resulting crystals were filtered and the mother liquor was evaporated (same precaution as indicated above), leaving the pure major diastereoisomer.

These compounds could be preserved for several months at –20 °C (even for three years for **6**).

(–)-(*R*)-3-Methoxy-10a-methyl-5,6,7,8,10,10a-hexahydro-phenanthrene-1,4-dione (4): To a solution of sulfinylquinone (*S*)-**2** (290 mg, 1.00 mmol, 1.0 equiv.) in anhydrous CH_2Cl_2 (10 mL), under argon, 2-vinyl-1-cyclohexene (**3**; 216 mg, 2.00 mmol, 2.0 equiv.) was added. After 10–12 d at room temp., the solvent was evaporated to give the crude cycloadduct **6**. Flash chromatography on demetallated silica gel (gradient elution cyclohexane/CH_2Cl_2/acetone, 2:1:1) afforded pure (*S*)-**4** as a yellow oil (15%). The yield could be improved by dissolving **6** in pyridine and allowing the sulfinyl group to spontaneously eliminate at room temp. (194 mg, 75%). R_f = 0.43 (cyclohexane/CH_2Cl_2/acetone, 2:2:1); the absolute stereochemistry was deduced from the known models and the X-ray analysis of cycloadduct **6**. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.97 (s, 1 H, MeOC=C*H*), 5.92 (m, 1 H, C=C*H*), 3.85 (s, 3 H, OCH_3), 2.95–2.30 (m, 8 H, 4 × CH_2), 2.10–1.81 (m, 2 H, CH_2), 1.25 (s, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 201.7 (C=O), 199.1 (C=O), 181.9 (C_{quat}), 164.0 (C_{quat}), 143.7(C_{quat}), 136.6 (C_{quat}), 135.0 (C_{quat}), 124.7 (MeOC=*C*H), 109.7 (C=*C*H), 56.6 (OCH_3), 40.5 (CH_2), 30.9 (CH_2), 29.7 (CH_2), 26.9 (CH_2), 23.8 (CH_3), 22.2 (CH_2) ppm. $[\alpha]_D^{20}$ = –23.2 (*c* = 0.42, CH_2Cl_2). $C_{16}H_{18}O_3$ (258.32): calcd. C 74.40, H 7.02; found C 74.31, H 6.89.

(–)-(4a*S*,4b*R*,10a*R*)-3-Methoxy-10a-methyl-5,6,7,8,10,10a-hexahydro-phenanthrene-1,4(4a*H*,4b*H*)-dione (10): To a solution of **6** (100 mg, 0.25 mmol) in MeOH (10 mL) at –20 °C, was added a wet slurry of Raney-Ni (2800 purchased from Aldrich, ca. 10 mg), and the resulting suspension was stored in a fridge at –20 °C for 12 h. The mixture was then carefully filtered through Celite, and the solvent was evaporated. Purification by flash chromatography (gradient elution cyclohexane/Et_2O, 1:1) afforded pure (*S*)-**10** as a colorless foam (43 mg, 70%). R_f = 0.5 (Et_2O). ^{1}H NMR (400 MHz, C_6D_6): δ = 5.42 (s, 1 H, MeOC=C*H*), 5.14 (m, 1 H, C=CH), 2.55 (d, *J* = 8.2 Hz, 1 H, COCH), 2.47 (ddd, *J* = 12, 5, 4 Hz, 1 H, =CCH), 2.35–2.21 (m, 3 H, CH_2), 2.00 (m, 1 H, CH_2), 1.78 (m, 1 H, CH_2), 1.60–1.54 (m, 2 H, CH_2), 1.35 (m, 1 H, CH_2), 1.13 (m, 1 H, CH_2), 0.98 (s, 3 H, CH_3), 0.62 (dddd, *J* = 28, 12, 8, 1.5 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, C_6D_6): δ = 201.8 (C=O), 194.1 (C=O), 163.3 (MeO-C_{quat}), 138.3 (HC=C_{quat}), 116.3 (=CH), 108.7 (=CH), 59.7 (COCH), 55.3 (OCH_3), 48.4 (C_{quat}), 35.6 (CH_2), 34.9 (CH), 34.4 (CH_2), 33.7 (CH_2), 28.2 (CH_2), 26.3 (CH_2), 20.5 (CH_3) ppm. $[\alpha]_D^{20}$ = –1 (*c* = 1.15, CH_2Cl_2). HRMS (EI): calcd. for $C_{16}H_{20}O_3Na$ [M]$^{+\cdot}$ 283.130; found 283.130. $C_{16}H_{20}O_3$ (260.33): calcd. C 73.82, H 7.74; found C 73.91, H 7.88.

The relative stereochemistry was confirmed by NOESY experiments.

(2*S*,6a*S*,10a*R*,10b*S*)-2-(Furan-3-yl)-9-methoxy-6a-methyl-10a-[(*S*)-(*p*-tolylsulfinyl)]-6,6a,10a,10b-tetrahydro-1*H*-benzo[*f*]isochromene-7,10(2*H*,4*H*)-dione (12β-12a): The reaction of quinone (*S*)-**2** with (*S*)-**7a** (2 equiv.) gave pure 12β-**12a** (340 mg, 72%). Reaction time: 6 d, temperature: –20 °C. Yellow, waxy oil. ^{1}H NMR (300 MHz, CD_2Cl_2, –20 °C): δ = 7.50–7.20 (m, 6 H, ArH), 5.94 (s, 1 H, MeO=C*H*), 5.39 (m, 1 H, =CH), 5.26 (m, 1 H, CHO), 4.30 (d, *J* = 14.2 Hz, 1 H, OCH_2), 4.23 (d, *J* = 14.2 Hz, 1 H, OCH_2), 3.53 (s, 3 H, OCH_3), 3.16 (td, *J* = 12.8, 5.5 Hz, 1 H), 2.42 [s, 3 H, CH_3 (*p*Tol)], 2.37–2.34 (m, 3 H, CH_2), 2.04 (d, *J* = 19.8 Hz, 1 H, CH_2), 1.52 (s, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, CD_2Cl_2, –20 °C): δ = 197.1 (C=O), 187.1 (C=O), 160.9 (C_{quat}), 142.9 (C_{quat}), 140.4 (C_{quat}), 135.0 (C_{quat}), 134.1 (C_{quat}), 129.7 (CH), 128.7 (CH), 127.4 (CH), 126.3 (2× CH_{arom}), 116.3 (CH), 110.0 (CH), 82.6 (C_{quat}), 73.8 (CH), 65.4 (CH_2), 56.3 (OCH_3), 52.1 (C_{quat}), 39.6 (CH_2), 28.6 (CH_2), 26.9 (CH_2); 21.4 [CH_3 (*p*Tol)], 16.5 (CH_3) ppm. IR (neat): $\tilde{\nu}$ = 3313 (br), 3142 (w), 1712 (w), 1662 (s), 1607 (s), 1504 (m), 1453 (m), 1358 (m), 1237 (s), 1205 (s), 1080 (s), 1037 (br), 955 (m), 875 (m), 810 (m), 709 (m) cm^{-1}.

(+)-(2*S*,6a*R*,10a*R*,10b*R*)-2-(Furan-3-yl)-9-methoxy-6a-methyl-6,6a,10a,10b-tetrahydro-1*H*-benzo[*f*]isochromene-7,10(2*H*,4*H*)-dione (12β-13a): To a solution of compound 12β-**12a** (100 mg, 0.25 mmol) in MeOH (10 mL) at –20 °C, was added a wet slurry of Raney-Ni (2800 purchased from Aldrich, ca. 10 mg), and the resulting suspension was stored in a fridge at –20 °C for 12 h. The mixture was then carefully filtered through Celite, and the solvent was evaporated. Purification by flash chromatography (gradient elution cyclohexane/Et_2O, 1:1) afforded pure 12β-**13a** (61 mg, 61%) as a pale-yellow amorphous powder. R_f = 0.5 (Et_2O). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37 (m, 1 H), 7.35 (t, *J* = 1.8 Hz, 1 H, ArH), 6.37 (m, 1 H, ArH), 5.81 (s, 1 H, MeOC=C*H*), 5.62 (m, 1 H, =CH), 4.63 (dd, *J* = 11.3, 1.6 Hz, 1 H, OCH), 4.25 (d, *J* = 12.5 Hz, 1 H, OCH_2), 4.16 (dm, *J* = 12.4 Hz, 1 H, OCH_2), 3.79 (s, 3 H, OCH_3), 2.95 (m, 1 H), 2.78 (d, *J* = 9.8 Hz, 1 H, OCCH), 2.57 (ddd, *J* = 12.7, 4.6, 2.0 Hz, 1 H, CH_2), 2.51 (d, *J* = 20.0 Hz, 1 H, CH_2), 2.28 (ddt, *J* = 18.5, 5.7, 2.0 Hz, 1 H, CH_2), 1.30 (dt, *J* = 12.7, 11.4 Hz, 1 H, CH_2), 1.14 (s, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 202.4 (C=O), 194.7 (C=O), 163.1 (C_{quat}), 143.2 (C_{quat}), 139.1 (C_{quat}), 132.8 (C_{quat}), 126.7 (=CH), 119.3 (MeOC=*C*H), 109.1 (CH_{arom}), 108.7 (CH), 72.4 (COH), 72.3 (COH_2), 56.5 (OCH_3), 56.4 (=C*C*H), 48.2 (C_{quat}), 39.8 (CH_2), 33.1 (CH_2), 21.1 (CH_3) ppm. $[\alpha]_D^{20}$ = +67 (*c* = 1.15, CH_2Cl_2). IR (neat): $\tilde{\nu}$ = 2962 (m), 2844 (m), 1711 (m), 1661 (s), 1605 (s) cm^{-1}.

The spectroscopic data are identical to those previously reported for the racemic form.[18]

(+)-(2*S*,6a*R*)-2-(Furan-3-yl)-9-methoxy-6a-methyl-6,6a-dihydro-1*H*-benzo[*f*]isochromene-7,10(2*H*,4*H*)-dione (12β-14a): A *syn*-desulfination was observed when the cycloadduct 12β-**12a** was stored in [D_5]pyridine at 4 °C after 2 d. Purification of the crude material by flash chromatography on silica gel (gradient elution cyclohexane to cyclohexane/Et_2O, 1:1) afforded pure 12β-**14b** (31 mg, 60%) as a white amorphous solid. R_f = 0.4 (cyclohexane/Et_2O, 1:1). ^{1}H NMR (300 MHz, [D_5]pyridine): δ = 7.65–7.54 (m, 2 H, ArH), 7.19 (m, 1 H, ArH), 5.66 (br. s, 1 H, MeOC=C*H*), 5.22 (app br. s, 1 H, =CH), 4.46 (dd, *J* = 15.3, 4.3 Hz, 1 H, COH), 4.25–4.19 (m, 2 H, COH_2), 3.41 (s, 3 H, OCH_3), 2.59–2.48 (m, 2 H, CH_2), 2.33 (m, 1 H, CH_2), 230–2.25 (m, 1 H, CH_2), 1.22 (s, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, [D_5]pyridine): δ = 202.2 (C=O), 194.3 (C=O), 167.3 (C_{quat}), 142.3 (C_{quat}), 133.1 (C_{quat}), 128.7 (CH_{arom}), 126.5 (CH_{arom}), 118.4 (=CH), 108.9 (=CH), 79.4 (OCH), 72.8 (OCH_2),

56.4 (OCH_3), 48.2 (C_{quat}), 41.0 (CH_2), 33.1 (CH_2), 18.0 (CH_3) ppm. $[\alpha]_D^{20}$ = +51 (*c* = 1, $CHCl_3$). $C_{19}H_{18}O_5$ (326.35): calcd. C 69.93, H 5.56; found C 69.99, H 5.43.

General Method for Lipase-Catalyzed Hydrolysis: The substrate (40 mmol) was dissolved in a mixture of pH 7.0 phosphate buffer (200 mL) and DMSO (20 mL) containing 5% (w/v) silica gel, at 40 °C. The enzyme (*Pseudomonas cepacia*) was added, and the pH was maintained at 7.0 by titration with 1 N aqueous NaOH. The progress of the reaction was followed by gas chromatographic analysis of aliquots taken from the reaction mixture at intervals. When the reaction was complete or the desired conversion was reached, the reaction mixture was filtered through silica gel and extracted three times with diethyl ether. The combined organic extracts were washed with saturated aqueous $NaHCO_3$ and brine, dried with $MgSO_4$ and concentrated in vacuo. The acetate and alcohol were separated by flash chromatography over silica gel (pentane/diethyl ether, 1:1).

General Method for Lipase-Catalyzed Transesterification:[32] THF (0.1 M), vinylacetate (10 equiv.) and substrate (90 mmol, 1 equiv.) were placed in a 500 mL screw-cap bottle and stirred gently at 35 °C. The enzyme (*Pseudomonas cepacia*) was added (1 equiv. w/w), and the reaction vessel was closed. The progress of the reaction was followed by gas chromatographic analysis of samples taken from the reaction mixture at intervals. When the reaction was complete or the desired conversion was reached, the reaction mixture was filtered through silica gel and the solvent was removed in vacuo. The acetate and alcohol were separated by flash chromatography over silica gel (cyclohexane/diethyl ether, 1:1).

(–)-(*S*)-1-(Furan-3-yl)but-3-en-1-ol (a): Following the general procedure described above, compound **a** was obtained as a clear, colorless oil (2.88 g, 46%). The *S* absolute stereochemistry was determined by comparison of the sign of optical rotation with reported literature values.[7] $[\alpha]_D^{20}$ = –30 (*c* = 1.72, CH_2Cl_2) {ref.[32] $[\alpha]_D^{20}$ = –30.7 (*c* = 1.72, CH_2Cl_2)}; >95% *e.e.*

(–)-(*S*)-3-[1-(Prop-2-ynyloxy)but-3-enyl]furan (d): To a flask charged with NaH (60% dispersion in mineral oil; 0.984 g, 24.6 mmol) in anhydrous toluene (30 mL) under an atmosphere of argon, was added a solution of (*S*)-1-(furan-3-yl)but-3-en-1-ol (**a**; 2 g, 14.5 mmol) in toluene (10 mL) at 0 °C under vigorous stirring. The mixture was warmed to room temperature and stirred for 1.5 h before being cooled to 0 °C and 15-crown-5 (1.4 mL, 7.2 mmol) was added slowly. The reaction mixture was warmed to room temperature and stirred for 0.5 h. After cooling again to 0 °C, propargyl bromide (80 wt.-% in toluene, 7.5 mL, 50.6 mmol) was added dropwise and the reaction was stirred for 2 h at room temperature. The reaction was quenched at 0 °C with ice-water (30 mL) and diluted with Et_2O (30 mL). The aqueous layer was extracted with Et_2O (2 × 30 mL) and the combined organic layers were washed with saturated aqueous $Na_2S_2O_3{\cdot}5H_2O$ (20 mL), water (20 mL), and brine (20 mL), dried with $MgSO_4$, filtered, and concentrated in vacuo. The resulting brown oil was purified by flash chromatography (toluene/cyclohexane, 5:95) to afford **d** (2.18 g, 85%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.40 (m, 2 H, ArH), 6.39 (t, *J* = 1.1 Hz, 1 H, ArH), 5.77 (ddt, *J* = 17.2, 10.2, 6.9 Hz, C*H*=CH_2), 5.08 (dm, *J* = 17.2 Hz, 1 H, CH=CH_2), 5.04 (dm, *J* = 10.2 Hz, 1 H, CH=CH_2), 4.56 (t, *J* = 6.8 Hz, 1 H, CHO), 4.13 (dd, *J* = 15.8, 2.4 Hz, 1 H, CH_2-C≡), 3.93 (dd, *J* = 15.8, 2.4 Hz, 1 H, CH_2-C≡), 2.57–2.65 (m, 1 H, CH_2), 2.41–2.49 (m, 1 H, CH_2), 2.40 (t, *J* = 2.4 Hz, 1 H, C≡CH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 143.6 ($CH_{arom.}$), 140.8 ($CH_{arom.}$), 134.3 (*C*=CH_2), 124.6 (C_{Arom}), 117.3 (C=*C*H_2), 108.7 ($CH_{arom.}$), 79.9 (CHO), 74.2 (*C*≡CH), 72.1 (C≡*C*H), 55.2 (CH_2), 40.6 (CH_2) ppm. $[\alpha]_D^{20}$ = –107 (*c* = 1.45, CH_2Cl_2). IR (neat): $\tilde{\nu}$ = 3294, 3077, 2907 (s), 2857, 1642, 1502, 1159, 1072, 1020, 917 cm^{-1}. MS (EI): *m*/*z* (%) = 176 (7) [M], 135 (100), 95 (41), 91 (17), 77 (43).

General Procedure for Enyne Metathesis Using Grubbs' 1st Generation Catalyst: To a stirring solution of Grubbs' 1st generation catalyst (0.1–0.2 mmol, 2 mol-%) in distilled and degassed (argon, 10 min and ethylene, 5 min) CH_2Cl_2 (10–20 mL), was added enyne (1–2 g, 5.8–12.5 mmol) dissolved in CH_2Cl_2 (3 mL). The solution was purged with ethylene gas for 10 min and stirred under an ethylene atmosphere at 100 °C (2–4 atm) for 10 min under microwave irradiation (20 mL sealed vial) or overnight at room temperature. The catalyst was quenched with the addition of ethyl vinyl ether (2 mL), and the solvent was removed in vacuo. The resulting brown oil was purified by flash chromatography (EtOAc/hexanes, 1:30) to afford the semicyclic 1,3-diene as a colorless oil. Most of the time, the dienes proved to be unstable to air/water upon prolonged storage and were, therefore, refrigerated (–15 °C) under an inert atmosphere, which allowed storage for several months.

(–)-(*S*)-2-(Furan-3-yl)-5-vinyl-3,6-dihydro-2*H*-pyran [(*S*)-7a]: Following the general procedure, the corresponding diene (*S*)-**7a** (163 mg, 93%) was obtained as a yellow oil. The absolute stereochemistry was determined from the sign of the optical rotation, which was opposite to that reported in the literature.[12] ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.43 (m, 1 H, ArH), 7.40 (t, *J* = 1.6 Hz, 1 H, ArH), 6.44 (s, 1 H, ArH), 6.29 (dd, *J* = 11.2, 10.8 Hz, 1 H, C*H*=CH_2), 5.90 (m, 1 H, =CH), 4.99 (d, *J* = 4.0 Hz, 1 H, CH=CH_2), 4.95 (d, *J* = 10.8 Hz, 1 H, CH=CH_2), 4.54 (dd, *J* = 10.0, 4.0 Hz, 1 H, CHO), 4.43 (m, 2 H, CH_2O), 2.48 (m, 1 H, CH_2), 2.37 (d, *J* = 18.4 Hz, 1 H, CH_2). $[\alpha]_D^{20}$ = –163 (*c* = 1.16, $CHCl_3$) {lit.[19b] $[\alpha]_D^{20}$ = +167.9 (*c* = 1.16, $CHCl_3$)}.

Supporting Information (see footnote on the first page of this article): Experimental procedure for the preparation of dienes for (±)-**9a**,**b**; (±)-**7d** enantio-enriched **7a**–**c**; full analytical data for compounds **4**, **6**, **10**, **11**, **12a**–**c**, 12α-**13a**,**b**, 12β-**13a**–**c**, 12α-**14a**,**b**, and 12α-**14a**–**c**; ^{1}H and ^{13}C NMR spectra for **12d** and X-ray crystal structure of compounds **6**, **11**, 12α-**12a**, and 12β-**12b**.

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