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An Enantioselective Approach to Furanoeremophilanes: (+)-9-Oxoeuryopsin

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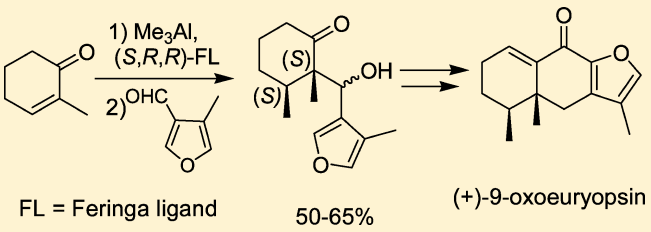
Supporting Information

ABSTRACT: An enantioselective total synthesis of the furanoeremophilane sesquiterpene (+)-9-oxoeuryopsin **1** is reported. The synthesis involves as a key step a copper(II) triflate catalyzed tandem asymmetric conjugate addition of $AlMe_3$ to 2-methyl-2-cyclohexen-1-one with the Feringa (*S*,*R*,*R*)-phosphoramidite binaphthol ligand, followed by aldol condensation of the resulting aluminum enolate with 4-methyl-3-furaldehyde **4**. This tandem transformation has not been previously reported with a 2-substituted-2-cyclohexen-1-one. Conventional functional group manipulations completed the synthesis.



INTRODUCTION

Members of the genera *Senecio*, *Euryops*, *Ligularia*, and *Psacalium* of the Asteraceae family are globally distributed plants rich in furanoeremophilane compounds.[1] This group of sesquiterpenes contains a linearly fused C_6–C_6–C_4O tricyclic (C_{12}) framework with three Me groups attached at the 4, 5, and 11 positions (Figure 1). Oxygenated functional groups at C-3,

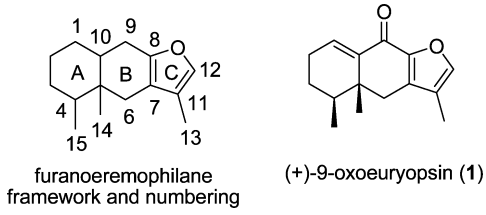


Figure 1. Furanoeremophilane framework and the structure of (+)-9-oxoeuryopsin.

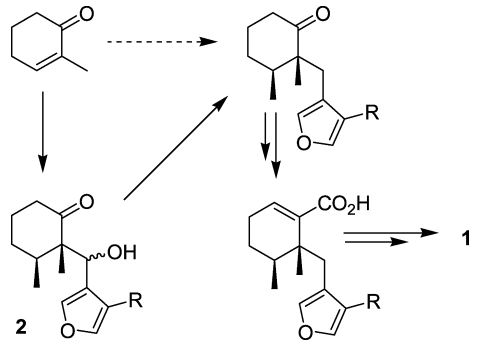
C-6, and C-9 are very common in these compounds. Reported biological profiles of furanoeremophilanes are diverse and include cytotoxic, antifungal, antifeedant, phytotoxic, anti-inflammatory, antibacterial, antihyperglycemic, and hepatotoxic activities.[2]

Syntheses of these natural products began in the late 1970s by Japanese researchers, but in particular Yamakawa and his group, which in a 7-year period synthesized dozens of furanoeremophilanes following a BC → ABC approach.[3] At present, all the known syntheses have been performed in the racemic series, although transformations among some natural furanoeremophilanes are also known.[4] Our interest in the total synthesis of these compounds started in 2004 with the successful synthesis of (±)-13-nor-9-oxoeuryopsin based on a convergent new approach by the novel A + C → A–C → A–B–C route.[5] The same strategy, but with a completely different set of chemical reactions, was published in the same year by White and Shanmugam with the synthesis of (±)-6β-hydroxyeuryopsin.[6] Now, we wish to present an asymmetric version of our approach which led us to the first total synthesis of a natural furanoeremophilane, (+)-9-oxoeuryopsin **1**.[7]

RESULTS AND DISCUSSION

Our synthetic route is shown in Scheme 1 and uses in the first step as the key reaction the well-known tandem[8] 1,4 alkyl

Scheme 1. Synthesis Plan



conjugate addition–enolate trapping reaction with an aldehyde to construct the A–C aldol intermediate **2** with a regio- and stereocontrolled introduction of the C-4 and C-5 methyl groups. Free-radical removal of the alcohol, homologation to the unsaturated carboxylic acid and a Friedel–Crafts cyclization completes the synthesis. A few comments about this approach are appropriate. First, it should be noted that for 9-

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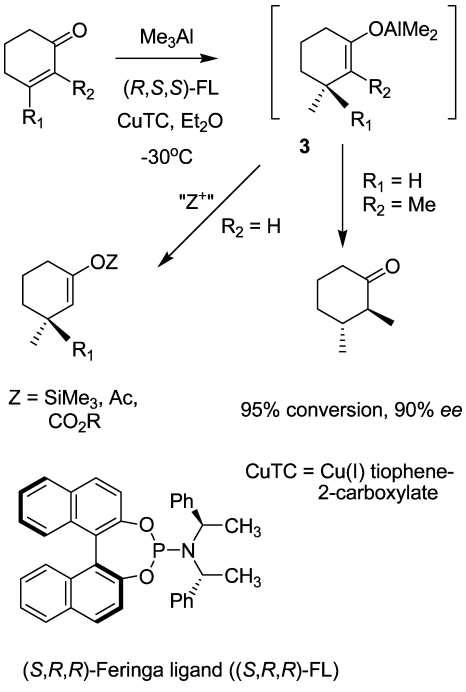
oxoeuryopsin synthesis, the apparently most convenient 3-halomethylfuran electrophiles in the enolate-trapping reaction cannot be employed due to the poor stability of the required electrophiles and the low yields (32−48%) and stereoselectivities (*cis*/*trans* ratios of 5.5−3.0:1 for the cyclohexane methyl groups) observed in model studies in the racemic series. Second, although the reaction is highly stereoselective, in the racemic 13-nor series an unexpected stable conformer with an axial furyl substituted chain was obtained,[9] which at an undetermined stage of the synthesis changed to an equatorial conformation, allowing the construction of ring B. In spite of the presence of the new methyl group in the furan ring, we anticipate that similar behavior would be observed in the present case. Finally, although a deoxygenation step is required for the synthesis of **1** to remove the oxygen substituent at C-6, other natural furanoeremophilanes containing an oxygen substituent at this position are known, and are potential synthetic targets for future studies.

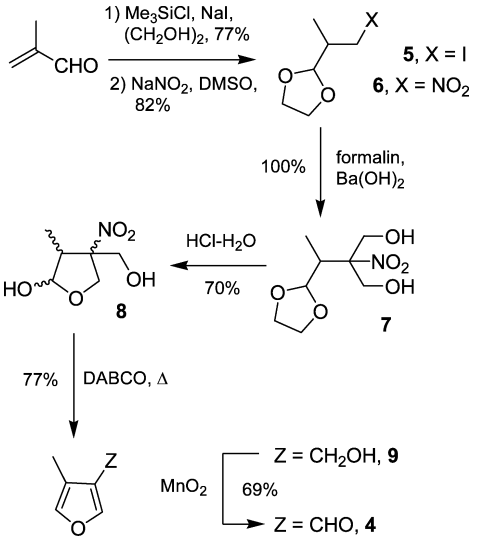
The copper-catalyzed asymmetric conjugate addition of zinc and aluminum reagents to enones in the presence of phosphoramidite binaphthol (mainly) and other ligands have been extensively investigated by Feringa, Alexakis, and Woodward.[10] The latter reagents are especially useful for α- and β-substituted enones which are unreactive toward zinc alkyls. Unfortunately, and in striking contrast to zinc enolates, the extension of this reaction to include trapping of aluminum enolates with aldehydes to form an additional C−C bond to give an aldol has been difficult to achieve due to the low reactivity of such species, as found by other authors.[11] Nevertheless, Alexakis and co-workers could trap the aluminum enolates from tandem conjugate addition of aluminum alkyls to 3-substituted enones only with oxyphilic electrophiles such as TMSCl or acid chlorides/anhydrides (Scheme 2).[12] The resulting TMS enol ethers, enol acetates, or mixed alkyl enol carbonates, though convenient enolate precursors require further isolation, purification and an additional reaction to form C−C bonds. For 2-methyl-2-cyclohexen-1-one, Vuagnoux−d'Augustin and Alexakis[12b] reported high conversions (>95%) and ee (90−93%) of (3*R*, 2*S*)-dimethylcyclohexanone with Me_3Al and the (*R*,*S*,*S*)-Feringa ligand ((*R*,*S*,*S*)-FL),[13] but trapping experiments with the intermediate aluminum enolate were not reported. Perhaps, since the results obtained with β-substituted enones were fruitless, the corresponding enolate trapping experiments with **3** (R_1 = H, R_2 = Me) to form C−C or C−O bonds were not attempted. Considering that the success of this reaction was key in our plan for the enantioselective synthesis of **1**, we decided to study the unreported trapping of the aforementioned intermediate enolate **3** with 4-methyl-3-furaldehyde **4**. However, it should be noted that for this study, the (*S*,*R*,*R*)-FL ligand is required to establish the 4*S* configuration of the natural product.

Aldehyde **4** is a known compound,[14] but we were unable to reproduce one of the most recent reported methods[14a] and a mixture with its regioisomer 2-methyl-3-furaldehyde was obtained. Hence, we designed a new method of synthesis of **4** based on previous work in our laboratory (Scheme 3).[15] The method starts from the known iodoketal **5** available in one step and at 77% yield from commercial methacrolein,[16] uses simple reactions and is easily performed in medium-sized batches. The volatile aldehyde **4** was obtained in 26% overall yield as a pale yellow oil, which was freshly distilled (bp 70 °C/20 mmHg) for the tandem reactions.

Scheme 2. Conjugate Addition−Enolate Trapping of 2- and 3-Substituted Cyclohexen-1-ones



Scheme 3. New Synthesis of 4-Methyl-3-furaldehyde 4



To our surprise and delight, even the first experiment afforded evidence of a successful tandem reaction in low yield and further experiments were needed for optimization (Scheme 4). Based on the assumption that conjugate addition of Me_3Al to 2-methyl-2-cyclohexen-1-one does not require any improvement, our entire efforts were focused on the aldehyde trapping step. We found it very important to dry the $Cu(OTf)_2$ immediately before use (2 h at 130 °C/20 mmHg), employ freshly distilled excess aldehyde (1.2 equiv) and inverse quenching (aqueous saturated NH_4Cl solution) of the reaction mixture to minimize aldol reversal. Other factors that can also be taken into account are thoroughly washing of the aluminum hydroxide precipitate with ether during the isolation procedure and the scale-up of the experiments. In the 30

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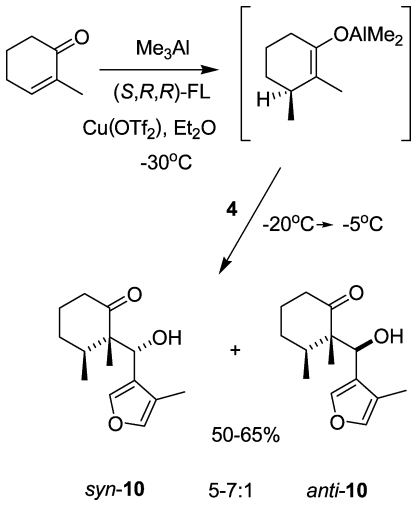
Scheme 4. Asymmetric Conjugate Addition of Me_3Al to 2-Methyl-2-cyclohexen-1-one and Trapping of the Aluminum Enolate with 4

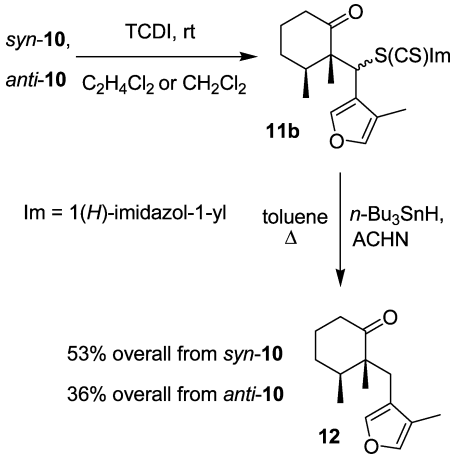


last optimized experiments with 300−500 mg batches of 2-methyl-2-cyclohexen-1-one (the limiting substrate), a reasonably constant 50−65% range of yields of the product was obtained, while an experiment with 700 mg had a reduced yield of 46%.

As in the 13-nor series, the aldol products could be separated by flash chromatography as major less polar (*syn*-**10**) and minor more polar (*anti*-**10**) products, the structures being assigned by X-ray crystal diffraction analysis of the latter isomer which shows the furyl containing substituent axially disposed. A quantitative determination of the ratio of aldols was not attempted, but isolated products were obtained in the range of 7−5:1. We believe that the real ratio is lower, because losses during purification of *anti*-**10** were higher compared with *syn*-**10**, due to the two column chromatographies required for the former.

The next step in the synthesis was removal of the OH function of the separated aldols by the Barton−McCombie protocol,[17] but we found unusual behavior of these compounds during preparation of the required substrates for the deoxygenation step (thiocarbonyl diimidazole (TCDI) in CH_2Cl_2 or $ClCH_2CH_2Cl$ at rt) (Scheme 5). For both isomers, the expected 1*H*-imidazol-1-yl *O*-carbothioates *syn*- and *anti*-**11a** were not found and a mixture of products were obtained instead in which the corresponding 1*H*-imidazol-1-yl carbodithioates *syn*- and *anti*-**11b** (IR 1051 cm^{-1}, C═S; MS 362, M^+) were the major components (56% and 48% from the *syn* and *anti* aldols, respectively). Although a search in SciFinder and the extensive listings of substrates in a recent review on the Barton−McCombie reaction[17b] revealed that alkyl 1*H*-imidazol-1-yl carbodithioates have not been submitted to the free radical conditions, from a mechanistic point of view it seemed feasible. This was indeed the case and compounds *syn*- and *anti*-**11b** were smoothly converted (n-Bu_3SnH and 1,1′-azobis(cyclohexanecarbonitrile) (ACHN) in toluene at 75 °C) to a single crystalline ketone **12**, mp 65−67 °C in 95% and 75% yields, respectively. X-ray diffraction analysis of this ketone by the anomalous dispersion method showed the expected (2*R*,3*S*) absolute configuration with an equatorial furyl containing chain as required for the synthesis (see the Supporting Information). This experiment demonstrates that

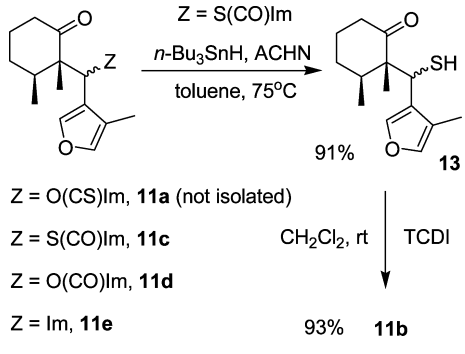
Scheme 5. Thiocarbonylation of Aldols 10 and Dedithiocarbonylation of 11b



the presence of the OH group in the chain is mandatory to stabilize the axial substituent in crystalline *anti*-**10**. Previously, Noyori and co-workers[18] had prepared aldols related to **10** (*syn*- and *anti*-3-ethyl-2-hydroxybenzylcyclohexan-1-one) and found by X-ray analyses that both diastereomers showed the same trans diaxial disposition of substituents as we observed with *anti*-**10**, which probably means this is a general phenomenon for this type of aldol. According to these authors, steric repulsion of the 2,3 substituents and multiple intermolecular hydrogen bonds combine to give the observed result. In our case, extensive intermolecular hydrogen bonding was also observed in the X-ray crystal analysis of *anti*-**10** (see the Supporting Information).

In the thiocarbonylation reaction of *syn*-**10**, we could also isolate and characterize the 1*H*-imidazol-1-yl S-carbothioate **11c** (12%; IR 1683 cm^{-1}, SC═O; MS 346, M^+), the 1*H*-imidazol-1-yl carboxylate **11d** (4%; IR 1759 cm^{-1}; MS 330, M^+) and the 1*H*-imidazol-1-yl derivative **11e** (13%; MS 286, M^+), but only the former was useful for the synthesis and could be converted into ketone **12** by (1) free-radical reduction to the thiol **13** (n-Bu_3SnH, ACHN, 91% yield), (2) TCDI reaction to **11b** (93% yield), and (3) free-radical hydrogen substitution of the 1*H*-imidazol-1-yl carbodithioate group as mentioned above (Scheme 6). To the best of our knowledge, the free radical conversion of the S-alkyl carbothioate group into a thiol (formally a deacylation) has no precedent in the literature. We have some spectroscopic evidence that *anti*-**10** gave a similar set of byproducts (*anti*-**11c−e**) in the thiocarbonylation reaction,

Scheme 6. Byproducts of the Thiocarbonylation of *syn*-10 and Preparation of 13



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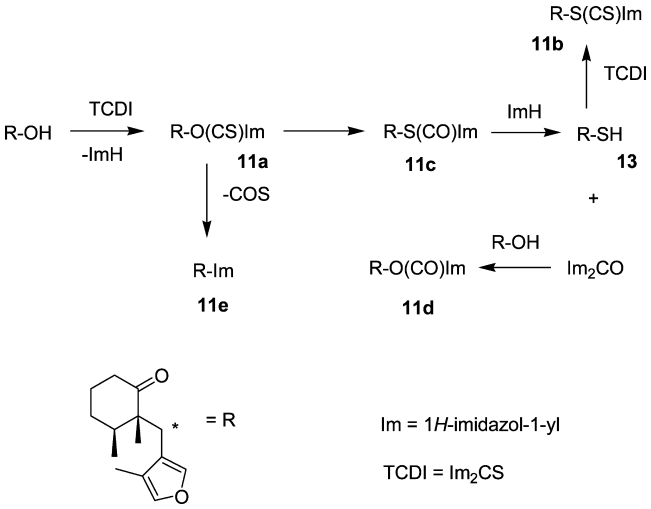
but the small amounts available of these compounds did not allow their satisfactory purification.

As mentioned above, MS and IR spectroscopy were crucial for the elucidation of structures of *syn*-**11b**-**e**, but chemical shifts in ^{1}H- and ^{13}C NMR for the "benzylic" CH and carbonyl or thiocarbonyl groups were also diagnostic for the assignments. In particular, it should be noted the ^{13}C chemical shift of the dithioate carbon at δ ~200.

With regard the reaction mechanism of these unusual transformations we have speculated a ionization-recombination process on the initially formed (but not found) O-alkyl 1*H*-imidazol-1-yl carbothioate *syn*-**11a**, as depicted in Scheme 7. A

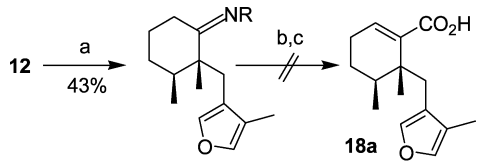
Scheme 7. Mechanistic Proposal for Formation of *syn*-11b−e



facile, furan-assisted Schönberg-type rearrangement[19] of *syn*-**11a** gives *syn*-**11c** which is cleaved by imidazole to thiol **13** and carbonyl diimidazole (CDI). TCDI reaction on **13** then gave *syn*-**11b** and CDI reaction of starting aldol affords *syn*-**11d**. The 1*H*-imidazolyl compound *syn*-**11e** should be formed as an alternative pathway (COS extrusion−imidazole recombination) during the Schönberg-type rearrangement. Evidence for this mechanism are the isolation of small amounts of thiol **13** in some of our experiments and the known precedent on the preparation of type **11e** compounds during thiocarbonylation or carbonylation of ferrocenyl alcohols.[20] Hence, the electron-rich ferrocenyl and furyl substituents are key for the anomalous observed results. Other electron-rich substituents from which we can expect the formation of rearranged products are conceivable and apparently this is the case for the bis 4-methoxy benzhydryl alcohol used as substrate in a solid state O-alkyl 1*H*-imidazol-1-yl carbothioate synthesis[21] which is reported to have a 1697 cm^{-1} band absorption in the IR. Clearly, this band belongs to the Schönberg rearranged S-alkyl 1*H*-imidazol-1-yl carbothioate isomer. From the above discussion and since intermediates in the Barton-McCombie deoxygenation are not always fully characterized, one can conclude that at least for substrates with electron donating R groups, perhaps many assumed ImC(S)OR compounds were actually ImC(S)SR compounds.[22]

In our original synthesis plan, we contemplated the use of the Shapiro reaction[23] on ketone **12** to simultaneously introduce the 1,10-double bond and C-9 as a carboxylic acid (Scheme 8). The required 2,4,6-triisopropylbenzenesulfonylhydrazone **14a** was prepared in moderate yield (43% with 33% recovered **12**)

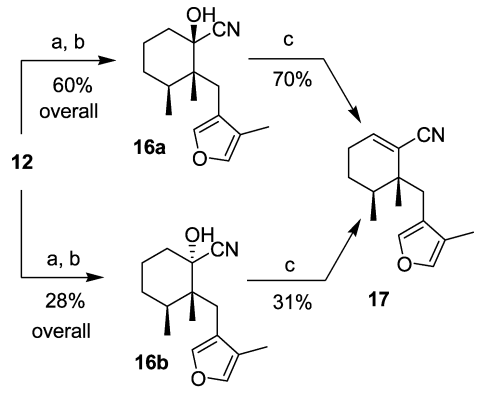
Scheme 8. Exploration of the Shapiro Reaction on 12



with aqueous 48% HBF_4 as the catalyst in THF−MeCN.[24] With anhydrous TsOH as the catalyst in THF, the yield of **14a** was only 8% with 33% recovered **12**, and if no catalyst was used, an 18% yield of **14a** was obtained. Under AcOH catalysis in EtOH, the azine derivative **14b** was obtained in 29% yield. The Shapiro reaction-CO_2 trapping of the intermediate carbanion was attempted with *n*-BuLi and *t*-BuLi alone or in the presence of TMEDA, but no evidence of an acid product was observed. It is conceivable that the acidity of the α hydrogens of the furan ring interfered with the intermediate vinyl carbanion formation. Hence, we abandoned this route and turned our attention to the longer reaction sequence employed successfully in the synthesis of (±)-13-nor-9-oxoeuryopsin.[5]

Ketone **12** was converted to a 3:1 mixture of *O*-trimethylsilyl-protected cyanohydrins **15a,b** by the method of Greenlee and Hangauer,[25] and the free cyanohydrins (10% HCl in THF at rt) **16a** and **16b** could be separated by column chromatography as crystalline solids mp 96−98 and 81 °C, respectively (Scheme 9). The more abundant, higher melting

Scheme 9. Preparation of Nitrile 17



point cyanohydrin **16a** had an equatorial β-OH as determined by single-crystal X-ray diffraction analysis. Both cyanohydrins could be dehydrated under the same reaction conditions to a single unsaturated nitrile **17** (70% and 31% yields, respectively), although substantial amounts of the starting cyanohydrins remained (13% and 43%, respectively) and ketone **12** was also recovered (7% each). The higher recovery of starting material and the lower yield of **17** obtained from **16b** is probably due to steric interference of the axial OH and the

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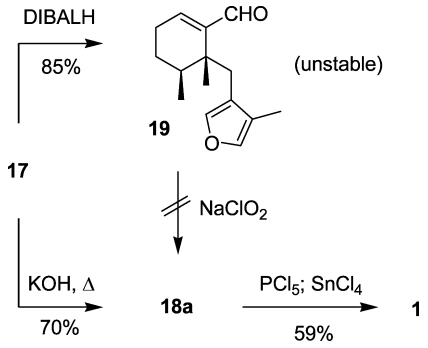
furyl group in the vicinal substituent, which makes it difficult to form the bulky dichlorophosphate leaving group.

Since in the 13-nor series we had observed that alkaline hydrolysis of the analogous unsaturated nitrile to the corresponding carboxylic acid was very sluggish (three cycles of 72 h reflux each, with KOH in diethyleneglycol−water), for the preparation of acid **18a** we first explored an alternative method through the unsaturated aldehyde **19** (Scheme 10).

Scheme 10. Last Steps of the Synthesis



This compound was obtained by DIBALH reduction of **17**, but it was very unstable and decomposed very rapidly during silica gel column chromatography. With basic alumina as the adsorbent,[6] an 85% yield of partially purified **19** was obtained, which was submitted immediately to oxidation conditions ($NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*-BuOH−THF−H_2O) and the crude acid fraction was treated with MeI and anhydrous K_2CO_3 in hot Me_2CO (35 °C), but only traces (2%) of the methyl ester **18b** were obtained. Fortunately, we were able to find an improved procedure for the alkaline hydrolysis of **17** (70% yield of **18a**) which reduces the reaction time to 24 h with just ethylene glycol as the solvent and KOH as the base (180 °C, 24 h). Some starting nitrile **17** was recovered (5.5%) along with traces of the intermediate amide.

To complete the synthesis, the crude acid **18a** was converted into (+)-9-oxoeuyopsin **1** in 59% overall yield by an intramolecular Friedel−Crafts cyclization ($SnCl_4$ as the Lewis acid) of the in situ formed acid chloride (PCl_5 in C_6H_6, rt). The mp of our synthetic sample was 124−125 °C (lit.[7] mp 119−120 °C) and showed optical rotations of $[\alpha]^{20}_{589}$ +6.5, $[\alpha]^{20}_{578}$ +8.7, $[\alpha]^{20}_{546}$ +16.9, $[\alpha]^{20}_{436}$ +158.5 (*c* 1.3 in $CDCl_3$) (lit.[7] $[\alpha]^{24}_{589}$ +0.35, $[\alpha]^{24}_{578}$ +2.8, $[\alpha]^{24}_{546}$ +7.1, $[\alpha]^{24}_{436}$ +9.65 (*c* 1.3 in $CDCl_3$)) and UV absorption at 291 nm (Et_2O, ε 25898) (lit.[7] λ_{max} 291 nm (ε 16200)). The higher values obtained by us suggest a higher purity of the synthetic material but unfortunately, a sample of natural 9-oxoeuryopsin for direct comparison is apparently no longer available. In order to conciliate the observed differences, we submitted our sample to X-ray diffraction analysis by the anomalous dispersion method, thus confirming the (4*S*,5*R*) assignment.

The electronic circular dichroism (ECD) spectroscopy is a widely used chiroptical method for assigning absolute configurations of synthetic or natural products. Unfortunately, ECD curves of furanoeremophilanes containing a cisoid enone system such as **1** have not (to our knowledge) been reported.[26] Hence, it was important for our future synthetic studies in this area to record the ECD curve of synthetic (4*S*, 5*R*)-**1**. The experimental curve in MeOH showed strong negative peaks at 213 and 267 nm ($\pi\pi^*$ forbidden and allowed transitions, respectively) and medium intensity positive peaks at 307 and 336 nm ($n\pi^*$ transitions) and was compared with the simulated ECD curves of (4*S*,5*R*)-**1** and its enantiomer (4*R*, 5*S*)-**1** acquired at the TD-PM6 theoretical level using Gaussian 09 software. The experimental curve is qualitatively similar to (4*S*, 5*R*)-**1** and as expected, a mirror image of (4*R*, 5*S*)-**1**.

CONCLUSIONS

In summary, we accomplished the first asymmetric total synthesis of a natural furanoeremophilane, (+)-9-oxoeuryopsin **1**, in 7% overall yield from 2-methyl-2-cyclohexen-1-one in seven relatively simple synthetic operations (conjugate addition-enolate trapping, imidazoylthiocarbonylation, bisdethiocarbonylation, protected cyanohydrin formation-hydrolysis, dehydration, alkaline hydrolysis, and Friedel−Crafts cyclization). To our knowledge, the key asymmetric copper-catalyzed conjugate addition of $AlMe_3$ to the poorly reactive 2-methyl-2-cyclohexen-1-one in the presence of the (*S*,*R*,*R*) Feringa ligand and trapping of the intermediate aluminum enolate with an aldehyde have not been previously reported. A new preparation of aldehyde **4** and the finding of unusual behavior of aldols **10** in the imidazoylthiocarbonylation reaction are also important contributions of our work. Further progress toward the total asymmetric syntheses of other furanoeremophilanes using this potentially general approach will be reported in due course.

EXPERIMENTAL SECTION

General Methods. TLC was performed on silica gel 60 GF_{254}, and flash chromatography was carried out on handpacked columns of silica gel 60 (230−400 mesh). The qualitative purity of all compounds was determined by TLC analysis using a UV lamp, iodine vapors, or a $KMnO_4$ solution stains for detection purposes.

^1H NMR spectra were recorded at 300, 400, or 500 MHz and ^{13}C NMR at 75, 100, or 125 MHz in $CDCl_3$ using TMS as internal standard (0.00 ppm). The signals in ^1H NMR are reported as s (singlet), d (doblet), t (triplet), q (quartet), h (heptuplet), m (multiplet), or brs (broad signal), followed by coupling constant(s) in Hz and integration. ^{13}C NMR spectra were recorded with ^1H decoupling and DEPT-135 experiments were performed to assign CH, CH_2, and CH_3. LRMS were carried out at 70 eV by electron-impact (EI) and HRMS were obtained by the FAB technique with a double sector mass spectrometer. Optical rotations were recorded on a digital polarimeter at room temperature.

Diethyl ether was dried by distillation from sodium/benzophenone ketyl. Commercial $Cu(OTf)_2$ was dried at 130 °C/20 mmHg for 3 h before use. 2-Methyl-2-cyclohexene-1-one was prepared by chlorination (SO_2Cl_2, CCl_4) or bromination (NBS, CCl_4) of 2-methylcyclohexanone and dehydrohalogenation with 2,4,6-collidine neat or LiBr/Li_2CO_3 in DMF, respectively.[27]

2-(1-Nitropropan-2-yl)-1,3-dioxolane 6.[28] A solution of iodoketal **5**[16] (17.4 g, 0.072 mol) in dry DMSO (5 mL) was added dropwise under Ar to a mixture of dry phloroglucinol (11 g, 0.087 mol) and dry $NaNO_2$ (9.9 g, 0.14 mol) in dry DMSO (70 mL). The dark solution was stirred at rt for 24 h, water/ice (∼100 g) was added, extracted with CH_2Cl_2, dried (Na_2SO_4), and concentrated at reduced pressure to give 18.37 g of a reddish oil. Column chromatography (8:2 hexane/AcOEt) gave nitroketal **6** (9.46 g, 82%) and 2-(propan-1-ol-2-yl)-1,3-dioxolane (1.55 g, 16%) which can be recycled through **5** (I_2, PPh_3, imidazole, CH_2Cl_2, 70%) or the corresponding *p*-toluenesulfonate (TsCl, Et_3N, CH_2Cl_2, 92%).

6: colorless oil; ^1H NMR (300 MHz, $CDCl_3$) δ 4.84 (d, J = 3.3 Hz, 1H), 4.57 (dd, J = 12.5, 5.6 Hz, 1H), 4.22 (dd, J = 12.5, 7.9 Hz, 1H,), 4.0−3.83 (m, 4H), 2.8−2.65 (m, 1H), 1.1 (d, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 104.6 (CH), 76.5 (CH_2), 65.3 (CH_2), 65.2 (CH_2), 36.2 (CH), 12.8 (CH_3); IR (film) ν 1553, 1379, 1117, 1070 cm^{-1}; LRMS (EI) m/z 161 (M^+), 73 (100), 45 (39); HRMS (FAB) m/z calcd for $C_6H_{12}NO_4$ $(M + H)^+$ 162.0766, found 162.0769.

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2-[1-(1,3-Dioxolan-2-yl)ethyl]-2-nitropropan-1,3-diol 7. A stirred mixture of nitroketal **6** (9.94 g, 0.062 mol) and 37% formalin (30 mL, 0.37 mol) was treated with $Ba(OH)_2$ (0.86 g, 2.7 mmol). An exothermic reaction was noted, and stirring was continued for 2 h at rt. It was extracted with AcOEt, washed with brine, dried (Na_2SO_4), and concentrated to dryness at reduced pressure to give the crude product (16.65 g). Column chromatography (50% → 60% → 70% AcOEt in hexane) afforded diol **7** (13.64 g, 100%).

7: clear viscous oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.92 (d, J = 3.9 Hz, 1H), 4.27 (d, J = 13.2 Hz, 2H), 4.14 (d, J = 13.2 Hz, 2H), 4.01−3.8 (m, 4H), 3.15−2.90 (brs, exchangeable 2 OH), 2.77 (dc, J = 7.2, 3.9 Hz, 1H), 1.02 (d, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 103.2 (CH), 95.5 (C), 65.3 (CH_2), 65.0 (CH_2), 63.5 (CH_2), 63.2 (CH_2), 40.8 (CH), 9.3 (CH_3); IR (film) ν 3500−2900, 1545, 1351, 1114, 1053, 946 cm^{-1}; LRMS (EI) m/z 220 (M-1)$^+$, 73 (100), 45 (25); HRMS (FAB) m/z calcd for $C_8H_{16}NO_6$ (M + H)$^+$ 222.0978, found 222.0977.

2-Hydroxy-4-hydroxymethyl-3-methyl-4-nitrotetrahydrofuran 8. A mixture of diol **7** (9.35 g, 0.04 mol) and 5% HCl (70 mL) in Me_2CO (300 mL) was heated under reflux for 27 h. It was cooled at 0 °C, a saturated solution of $NaHCO_3$ (80 mL) was added dropwise, and then solid $NaHCO_3$ in small portions until neutralization was complete. After removal of Me_2CO at reduced pressure, it was extracted with CH_2Cl_2 (3 × 50 mL) and AcOEt (3 × 50 mL). Each organic extract was separately dried (Na_2SO_4) and concentrated at reduced pressure to give 1.59 and 5.86 g of crude materials, respectively. Column chromatography (1:1 hexane/AcOEt) from the CH_2Cl_2 extract afforded cyclic hemiketal **8** (0.48 g). From the AcOEt extraction, after column chromatography (1:1 hexane/AcOEt) 4.8 g (71%) of **8** and 0.41 g (4.3%) of a cyclic mixed ketal which was not fully characterized, were obtained. As expected, the ^{1}H NMR spectrum of **8** (mixture of four diastereoisomers) is very complex, but we could assign the signals for one of the two major isomers (**8a**).

8: colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$, only the signals due to **8a** are given) δ 5.26 (t, J = 4 Hz, 1H), 4.64 (d, J_{AB} = 10.8 Hz, $1H_A$), 4.49−3.80 (m, 2H), 4.37 (d, J_{AB} = 10.8 Hz, $1H_B$), 3.75−3.65 (brs, exchangeable OH), 2.60−2.40 (brs, exchangeable OH), 2.29 (dq, J = 7.1, 3.9 Hz,1H), 1.06 (d, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, all signals are given) δ 104.2 (CH), 104.1 (CH), 100.2 (CH), 99.4 (C), 99.9 (CH), 98.3 (C), 97.8 (C), 96.6 (C), 72.3 (CH_2), 71.3 (CH_2), 71.1 (CH_2), 69.9 (CH_2), 65.0 (CH_2), 64.9 (CH_2), 63.0 (CH_2), 63.1 (CH_2), 47.5 (CH), 47.3 (CH), 46.9 (CH), 44.5 (CH), 11.6 (CH_3), 11.5 (CH_3), 8.8 (CH_3), 7.9 (CH_3); IR (film) ν 3700−3000, 1546, 1073, 1014, 938 cm^{-1}; LRMS (EI) m/z 160 (2), 130 (6), 113 (14), 101 (33), 83 (62), 67 (100), 55 (40); HRMS (FAB) m/z calcd for $C_6H_{11}NO_5$ (M$^+$) 177.0637, found 177.0640.

4-Methyl-3-furanmethanol 9. To a solution of cyclic hemiketal **8** (5 g, 0.028 mol) in dry DME (96 mL) was added DABCO (3.81 g, 0.034 mol) and the mixture heated at reflux for 24 h. Solvent was removed at reduced pressure, water was added, and the product was extracted with CH_2Cl_2 and washed with 10% HCl, a saturated solution of $NaHCO_3$, and brine. After drying (Na_2SO_4), the solvent was removed to afford a quantitative yield of **9** (3.16 g). Column chromatography (75:25, hexane/AcOEt) of 1.21 g of crude alcohol gave the pure product (1 g, 77%). In small batches, purification of crude **9** by Kugelrohr distillation (90 °C/20 mmHg) affords yields up to 82% yield, but in large batches extensive decomposition was observed even at 70°/5 mmHg. Even in the freezer, pure furanmethanol **9** is unstable if kept neat but is stable in acetone solution for months.

9: colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37−7.35 (m, 1H), 7.20−7.17 (m, 1H), 4.50 (s, 2H), 2.05 (d, J = 0.9 Hz, 3H), 1.48−1.40 (brs, exchangeable OH); ^{13}C NMR (75 MHz) δ 140.6 (CH), 140.2 (CH), 125.2 (C), 120.0 (C), 55.4 (CH_2), 7.8 (CH_3); IR (film) ν 3600−3000, 1550, 1451, 1139, 1043, 1004, 873, 798, 756 cm^{-1}; LRMS (EI) m/z 112 (M$^+$, 100), 95 (27), 94 (61), 55 (43), 32 (36).[14c]

4-Methyl-3-furaldehyde 4. (a) With MnO_2: Commercial MnO_2 (41.6 g, 0.48 mol) was added in portions to a stirred solution of **9** (3.16 g, 0.028 mol) in CH_2Cl_2 (120 mL) and the suspension stirred at rt for 24 h. The suspension was filtered through Celite and the cake thoroughly washed with CH_2Cl_2. The solvent was removed at reduced pressure, and the crude aldehyde (2.47 g) was freshly distilled before use. Recovery of pure aldehyde after distillation was 70−72% yield independently of using pure **9** or more conveniently, crude furan alcohol precursor. (b) Swern oxidation: To oxalyl chloride (0.06 mL, 0.64 mmol) in dry CH_2Cl_2 (2 mL) cooled at −50 °C was added dry DMSO (0.09 mL, 1.26 mmol). After the solution was stirred for 2 min, a solution of **9** (0.062 g, 0.55 mmol) in dry CH_2Cl_2 (0.7 mL) was added, and after 15 min dry Et_3N (0.4 mL, 2.9 mmol) was added. The resulting mixture was then allowed to reach rt, H_2O (5 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were washed (5 mL each) with brine, 1% HCl, H_2O, 5% aqueous Na_2CO_3, and H_2O. After drying (Na_2SO_4), the solvent was removed at reduced pressure (150 mmHg), and the residual dark brown oil was distilled in a Kugelrohr apparatus (68−70 °C/20 mmHg) to provide 0.041 g (0.37 mmol, 66%) of pure **4**.

4: pale yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.98 (d, J = 0.6 Hz, 1H), 7.98 (d, J = 1.8 Hz, 1H), 7.26−7.23 (m, 1H), 2.24 (d, J = 1.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 185.5 (C), 152.8 (CH), 141.9 (CH), 127.8 (C), 119.2 (C), 8.8 (CH_3); IR (film) ν 1688, 3139, 1538, 1145, 1043, 875, 824, 754 cm^{-1}; LRMS (EI) m/z 110 (M$^+$, 100), 109 (99), 81 (9), 53 (31).[14c]

Tandem Conjugate Addition−Aldol Formation. Preparation of *syn*-10 and *anti*-10. A Schlenk type tube flask was charged with freshly dried (130 °C/20 mmHg, 1−2 h) $Cu(OTf)_2$ (0.014 g, 0.04 mmol) and (*S*,*R*,*R*)-FL (0.041 g, 0.076 mmol). The system was evacuated and filled with dry Ar (three cycles), and dry Et_2O (10 mL) was added. The mixture was stirred 1 h at rt and cooled at −30 °C, and a 2 M solution of Me_3Al in toluene (3.2 mL, 6.4 mmol) was added. After the mixture was stirred for 15 min, a solution of 2-methyl-2-cyclohexen-1-one (0.36 g, 3.2 mmol) in dry Et_2O (4 mL) was added (3 mL of dry Et_2O was used for rinsing). The reaction mixture was stirred at −30 °C for 18 h, and a solution of aldehyde **4** (0.43 g, 3.8 mmol) in dry Et_2O was added (3 mL of dry Et_2O for rinsing). The mixture was stirred at −20 °C for 2 h and at −5 °C for 30 min, and the green solution poured into saturated NH_4Cl solution (18 mL). After 4 h of stirring at rt, the color of the solution changed to white and finally blue. The suspension was filtered, the cake thoroughly washed with Et_2O and after the usual workup the crude material was obtained (0.87 g). Column chromatography (10% → 15% → 20% → 30% AcOEt in hexane) gave *syn*-**10** (0.45 g, 60%) and impure *anti*-**10** (0.091 g). Final purification of *anti*-**10** required another column chromatography (85:15 hexane/Me_2CO) to get the pure product (0.064 g, 8%). Other compounds isolated were the phosphoramidate ligand (67%) and the chiral binaphthol (7%).

*(2S,3S)-2-((R)-Hydroxy(4-methylfuran-3-yl)methyl)-2,3-dimethylcyclohexanone (syn-**10**):* colorless solid; mp 30−32 °C; R_f = 0.50 (7:3, hexane/AcOEt); $[\alpha]^{21}_D$ = +42.2 (c 1.46 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17−7.14 (m, 2H), 4.40 (d, J = 11 Hz, 1H), 3.94 (d, J = 11 Hz, exchangeable OH), 2.54−2.44 (m, 1H), 2.37−2.28 (m, 1H), 2.02 (d, J = 0.8 Hz), 1.99−1.89 (m, 2H), 1.65−1.54 (m, 3H), 1.38 (s, 3H), 0.86 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 219.9 (C), 140.6 (CH), 139.2 (CH), 126.1 (C), 120.4 (C), 70.7 (CH), 55.8 (C), 39.4 (CH_2), 36.9 (CH), 29.7 (CH_2), 24.0 (CH_2), 17.1 (CH_3), 15.1 (CH_3), 8.2 (CH_3); IR (KBr) ν 3600−3100, 1692, 1456, 1051, 1012, 807, 787 cm^{-1}; LRMS (EI) m/z 236 (M$^+$, 2), 126 (77), 111 (100); HRMS (FAB) m/z calcd for $C_{14}H_{21}O_3$ (M + H)$^+$ 237.1491, found 237.1490.

*(2S,3S)-2-((S)-Hydroxy(4-methylfuran-3-yl)methyl)-2,3-dimethylcyclohexanone (anti-**10**):* colorless solid; mp 83−84 °C; R_f = 0.43 (7:3, hexane/AcOEt); $[\alpha]^{21}_D$ = +41.2 (c 1.0 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, J = 1.6 Hz, 1 H), 7.15 (q, J = 1.2 Hz, 1 H), 4.66 (d, J = 8.4 Hz, 1 H), 3.0 (d, J = 8.4 Hz, exchangeable OH), 2.57 (ddd, J = 12.8, 11.2, 6.0 Hz, 1 H), 2.42- 2.3 (m, 2 H), 2.04−2.0 (m, 1 H), 2.02 (d, J = 0.8 Hz, 3 H), 1.87−1.54 (m, 3 H), 0.99 (d, J = 6.8 Hz, 3 H), 0.96 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 218.0 (C), 141.8 (CH), 139.0 (CH), 126.0 (C), 120.1 (C), 68.5 (CH), 57.1 (C), 39.3 (CH_2), 38.6 (CH), 29.8 (CH_2), 26.0 (CH_2), 15.47 (CH_3), 14.6 (CH_3), 8.52 (CH_3); IR (KBr) ν 3600−3300, 1692, 1455, 1058, 1034, 867, 800 cm^{-1}; LRMS (EI) m/z 236 (M$^+$, 8), 126 (67),111

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(100); HRMS (FAB) m/z calcd for $C_{14}H_{20}O_3$ (M^+) 236.1412, found 236.1413.

Imidazoylthiocarbonylation Reactions. (a) *syn*-**10** as substrate: Two identical batches of a solution of *syn*-**10** (0.21 g, 0.89 mmol) and TCDI (0.4 g, 2.2 mmol) in dry CH_2Cl_2 (1.5 mL) were stirred at rt for 5 h. The solvent was removed at reduced pressure, and the residues were combined and purified by column chromatography (30% → 40% → 50% AcOEt in hexane) to give (*syn*-**11b**) (0.36 g, 56%), (*syn*-**11c**) (0.057 g, 9%), (*syn*-**11d**) (0.069 g, 12%) and (*syn*-**11e**) (0.055 g, 11%).With 1,2-dichloroethane as solvent yield of *syn*-**11b** was lower (46%).

*(ζ)-((1R,2S)-1,2-Dimethyl-6-oxocyclohexyl)(4-methylfuran-3-yl)-methyl 1H-imidazole-1-carbodithioate (syn-**11b**):* yellow solid; mp 147−148 °C; R_f = 0.50 (1:1, hexane/AcOEt); $[\alpha]^{20}_D$ = −453 (c 0.71 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.52−8.50 (m, 1H), 7.81 (t, J = 1.5 Hz, 1H), 7.23 (d, J = 1.5 Hz, 1H), 7.12 (q, J = 1.5 Hz, 1H), 7.07 (dd, J = 1.5, 0.9 Hz, 1H), 5.66 (s, 1H), 2.51 (td, J = 14.4, 6.3 Hz, 1H), 2.42−2.33 (m, 1H), 2.04 (d, J = 1.5 Hz, 3H), 2.13−2.03 (m, 1H), 2.02−1.92 (m, 2H), 1.74−1.44 (m, 2H), 1.35 (s, 3H), 1.11 (d, J = 6.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.1 (C), 201.7 (C), 143.5 (CH), 139.4 (CH), 136.0 (CH), 130.6 (CH), 124.0 (C), 120.2 (C), 118.0 (CH), 59.4 (C), 50.9 (CH), 38.2 (CH_2), 37.7 (CH), 30.3 (CH_2), 24.4 (CH_2), 16.4 (CH_3), 15.7 (CH_3), 9.28 (CH_3); IR (KBr) ν 1697, 1461, 1367, 1272, 1216, 1052, 997, 821 cm^{-1} ; LRMS (EI) m/z 362 (M^+, 12), 219 (100); HRMS (FAB) m/z calcd for $C_{18}H_{23}N_2O_2S_2$ $(M + H)^+$ 363.1201, found 363.1198.

*S-(ζ)-((1R,2S)-1,2-Dimethyl-6-oxocyclohexyl)(4-methylfuran-3-yl)methyl 1H-imidazole-1-carbothioate (syn-**11c**):* brownish glassy solid; R_f = 0.44 (4:6 hexane/AcOEt); $[\alpha]^{20}_D$ = −140 (c 0.8 in $CHCl_3$); ^{1}H NMR (500 MHz) δ 8.27−8.25 (m, 1H), 7.49 (t, J = 1.5 Hz, 1H), 7.21 (d, J = 2 Hz, 1H), 7.15−7.14 (m, 1H), 7.1−7.09 (m, 1H), 4.94 (s, 1H), 2.53 (td, J = 14.2, 6.5 Hz, 1H), 2.41−2.35 (m, 1H), 2.10−2.02 (m, 1H), 2.03 (d, J = 1 Hz, 3H), 2.02−1.95 (m, 1H), 1.73−1.59 (m, 2H), 1.61−1.48 (m, 1H), 1.36 (s, 3H), 1.02 (d, J = 7 Hz, 3H); ^{13}C NMR (125 MHz) δ 214.2 (C), 168.5 (C), 143.0 (CH), 139.4 (CH) 135.5 (CH), 130.3 (CH), 124.1 (C), 119.9 (C), 116.0 (CH), 58.0 (C), 44.7 (CH), 38.3 (CH_2), 37.9 (CH), 30.3 (CH_2), 24.6 (CH_2), 17.2 (CH_3), 15.5 (CH_3), 8.2 (CH_3); IR (film) ν 1702, 1683, 1467, 1364, 1292, 1270, 1218, 1099, 1055, 888 cm^{-1} ; LRMS (EI) m/z 346 (M^+, 14), 219 (82), 95 (100); HRMS (FAB) m/z calcd for $C_{18}H_{23}N_2O_3S$ $(M + H)^+$ 347.1429, found 347.1429.

*(ζ)-((1S,2S)-1,2-Dimethyl-6-oxocyclohexyl)(4-methylfuran-3-yl)-methyl) 1H-imidazole-1-carboxylate (syn-**11d**):* brownish glassy solid; R_f = 0.35 (4:6 hexane/AcOEt); $[\alpha]^{20}_D$ = −1.75 (c 1.2 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.16−8.15 (m, 1H), 7.45 (d, J = 1.5 Hz, 1H), 7.43 (t, J = 1.5 Hz, 1H), 7.17 (q, J = 1.5 Hz, 1H), 7.06 (dd, J = 1.5, 0.5 Hz, 1H), 6.17 (s, 1H), 2.46 (ddd, J = 14.5, 10.0, 5.5 Hz, 1H), 2.37−2.30 (m, 1H), 2.12−2.04 (m, 1H), 2.08 (d, J = 1 Hz, 3H) 1.98−1.9 (m, 2H), 1.75−1.65 (m, 1H), 1.64−1.55 (m, 1H), 1.28 (s, 3H), 0.98 (d, J = 7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 211.5 (C), 148.5 (C), 143.3 (CH), 139.7 (CH), 137.2 (CH), 130.7 (CH), 120.8 (C), 120.2 (C), 117.2 (CH), 74.7 (CH), 56.8 (C), 39.6 (CH_2), 36.9 (CH), 29.4 (CH_2), 23.5 (CH_2), 16.0 (CH_3), 15.9 (CH_3), 8.55 (CH_3); IR (film) ν 1759, 1709, 1471, 1389, 1317, 1287, 1242, 1175, 1096, 1056, 1001, 948 cm^{-1} ; LRMS (EI) m/z 330 (M^+, 5), 219 (77), 111 (66), 95 (100); HRMS (FAB) m/z calcd for $C_{18}H_{23}N_2O_4$ $(M + H)^+$ 331.1658, found 331.1662.

*(2S,3S)-2-((ζ)-(1H-Imidazol-1-yl)(4-methylfuran-3-yl)methyl)-2,3-dimethylcyclohexanone (syn-**11e**):* colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$, ∼5:1 diastereoisomer mixture of *syn*-**11e-1** and *syn*-**11e-2**): *syn*-**11e-1** δ 7.53−7.52 (m, 1H), 6.98 (s, 1H), 6.89 (t, J = 1 Hz, 1H), 6.67 (d, J = 2 Hz, 1H), 6.55−6.53 (m, 1H), 5.34 (dd, J = 2.3, 1.0 Hz, 1H), 2.22−2.13 (m, 1H), 2.13−2.06 (m, 1H), 1.79−1.76 (m, 1H), 1.78 (d, J = 1.5 Hz, 3H), 1.60−1.54 (m, 1H), 1.48−1.22 (m, 2H), 1.12 (s, 3H), 0.84 (d, J = 7 Hz, 3H). *syn*-**11e-2** δ 7.54 (s, 1H), 7.07 (s, 1H), 6.87 (t, J = 1 Hz, 1H), 6.55−6.53 (m, 1H), 6.31 (d, J = 2 Hz, 1H), 5.59 (dd, J = 2.3 1.0 Hz, 1H), 2.6−2.51 (m, 1H), 2.37−2.22 (m, 1H), 2.13−2.06 (m, 1H), 2.06−1.76 (2H), 1.82 (d, J = 1.5 Hz, 3H), 1.6−1.42 (m, 1H), 1.12 (s, 3H), 0.82 (d, J = 7 Hz, 3H); ^{13}C NMR (125 MHz): *syn*-**11e-1** δ 213.0 (C), 145.8 (CH), 140.4 (C), 136.8 (CH), 129.8 (CH), 125.6 (CH), 117.5 (CH), 114.2 (C), 85.5 (CH), 54.5 (C), 41.9 (CH), 38.1 (CH_2), 28.8 (CH_2), 23.6 (CH_2), 19.6 (CH_3), 15.7 (CH_3), 7.8 (CH_3). *syn*-**11e-2** δ 212.7 (C), 145.9 (CH), 141.1 (C), 136.5 (CH), 129.6 (CH), 127.5 (CH), 117.1 (CH), 114.0 (C), 84.3 (CH), 54.6 (C), 43.8 (CH), 38.6 (CH_2), 28.7 (CH_2), 23.1 (CH_2), 18.9 (CH_3), 15.0 (CH_3), 7.7 (CH_3); IR (film) ν 1702, 1069 cm^{-1}; LRMS (EI) m/z 288 (M^++2, 6), 287 (M^+ + 1, 39), 286 (M^+, 59), 219 (100), 161 (80), 95 (65); HRMS (FAB) m/z calcd for $C_{17}H_{23}N_2O_2$ $(M + H)^+$ 287.1760, found 287.1758.

(b) *anti*-**10** as substrate: The same procedure as above was followed with *anti*-**10** (0.11 g, 0.46 mmol), TCDI (0.2 g, 1.13 mmol) and 1,2-dichloroethane (1.5 mL) for 15 h. Column chromatography (30% → 40% → 50% AcOEt in hexane) gave recovered starting material (0.009 g, 9%) and *anti*-**11b** (0.081 g, 48%). In this case, the yield of *anti*-**11b** was lower (40%) with CH_2Cl_2 as solvent.

*(epi-ζ)-((1R,2S)-1,2-Dimethyl-6-oxocyclohexyl)(4-methylfuran-3-yl)methyl 1H-imidazole-1-carbodithioate (anti-**11b**):* yellow oil; R_f = 0.54 (4:6, hexane/AcOEt); $[\alpha]^{20}_D$ = +71.8 (c 1.53 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.65−8.55 (m, 1H), 7.81 (t, J = 1.5 Hz, 1H), 7.60 (dd, J = 1.8, 0.3 Hz, 1H), 7.12−7.09 (m, 1H), 7.09 (dd, J = 1.5, 0.9 Hz, 1H), 5.42 (s, 1H), 2.56 (td, J = 13, 6 Hz, 1H), 2.35−2.29 (m, 1H), 2.29−2.21 (m, 1H), 2.17 (d, J = 1.2 Hz, 3H), 2.06−2.0 (m, 1H), 1.82−1.77 (m, 1H), 1.71−1.58 (m, 2H), 1.13 (d, J = 6.5 Hz, 3H); 1.1 (s, 3H), ^{13}C NMR (125 MHz, $CDCl_3$) δ 214.1 (C), 199.4 (C), 144.9 (CH), 138.8 (CH), 135.9 (CH), 130.6 (CH), 124.0 (C), 120.4 (C), 118.0 (CH), 59.0 (C), 49.2 (CH), 40.0 (CH), 38.3 (CH_2), 30.3 (CH_2), 25.8 (CH_2), 16.8 (CH_3), 16.3 (CH_3), 9.1 (CH_3); IR (film) ν 1704, 1464, 1367, 1271, 1221, 1051, 1003, 826 cm^{-1}; LRMS (EI) m/z 362 (M^+, 7), 219 (100), 95 (87); HRMS (FAB) m/z calcd for $C_{18}H_{23}N_2O_2S_2$ $(M + H)^+$ 363.1201, found 363.1205.

(c) Thiol **13** as substrate: The same procedure as above was followed with **13** (0.018 g, 0.07 mmol), TCDI (0.042 g, 0.24 mmol) in CH_2Cl_2 (0.2 mL) for 9 h. Column chromatography gave *syn*-**11b** (0.024 g, 93%).

Preparation of 12 and 13 by Dethiocarbonylation Reactions. (a) *syn*-**11b** as substrate: ACHN (0.046 g, 0.19 mmol) was suspended in a solution of *syn*-**11b** (0.22 g, 0.6 mmol) in toluene (2.2 mL) and sonicated while Ar was bubbled through the solution for 20 min. The reaction mixture was heated at 75 °C, *n*-Bu_3SnH (0.032 mL, 1.2 mmol) was added, and heating was continued for 2h. The solvent was removed at reduced pressure and the residue purified by column chromatography (98:2 hexane/AcOEt) to give **12** (0.127 g, 95%) mp 65−67 °C.

(b) *anti*-**11b** as substrate: The same procedure as above was followed with *anti*-**11b** (0.07 g, 0.2 mmol), ACHN (0.016 g, 0.065 mmol) and *n*-Bu_3SnH (0.11 mL, 0.4 mmol) in dry toluene (0.7 mL). After 3 h heating, removal of solvent and column chromatography (98:2 hexane/AcOEt) afforded **12** (0.033 g, 75%).

*(2R,3S)-2,3-Dimethyl-2-((4-methylfuran-3-yl)methyl)-cyclohexanone (**12**):* colorless prisms; mp 65−67 °C; R_f = 0.51 (85:15, hexane/AcOEt); $[\alpha]^{22}_D$ = +9.1 (c 1.01 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.13−7.12 (m, 1H), 7.06 (s, 1H), 2.83 (dd, J = 15, 0.75 Hz, 1H), 2.48 (d, J = 15 Hz, 1H), 2.42−2.37 (m, 2H), 2.01−1.88 (m, 2H), 1.95 (d, J = 1.5, 3H), 1.85−1.79 (m, 1H), 1.7−1.61 (m, 1H), 1.6−1.5 (m, 1H), 1.03 (s, 3H), 0.95 (d, J = 7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 215.7 (C), 141.4 (CH), 138.8 (CH), 121.3 (C), 121.9 (C), 53.5 (CH_3), 38.4 (CH_2), 37.7 (CH), 29.2 (CH_2), 29.2 ($ArCH_2$), 23.9 (CH_2), 19.0 (CH_3), 16.0 (CH_3), 8.4 (CH_3); IR (KBr) ν 1701, 1456, 1144, 1047, 801 cm^{-1}; LRMS (EI) m/z 220 (M^+, 10), 96 (77), 95 (100); HRMS (FAB) m/z calcd for $C_{14}H_{21}O_2$ $(M + H)^+$ 221.1542, found 221.1543.

(c) *syn*-**11c** as substrate: The same procedure as above was followed with **11c** (0.026 g, 0.076 mmol), ACHN (0.006 g, 0.023 mmol) and *n*-Bu_3SnH (0.04 mL, 0.15 mmol) in dry toluene (1.1 mL). After 9 h heating, column chromatography (9:1 hexane/AcOEt) afforded **13** (0.017 g, 91%) as a white solid.

*(2R,3S)-2-((ζ)-Mercapto(4-methylfuran-3-yl)methyl)-2,3-dimethylcyclohexanone (**13**):* colorless solid; mp 78−80 °C; R_f = 0.50 (85:15, hexane/AcOEt); $[\alpha]^{20}_D$ = −79.1 (c 0.66 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21−7.2 (m, 1H), 7.14−7.12 (m, 1H), 4.05 (d,

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J = 9.6 Hz, 1H), 2.41−2.28 (m, 2H), 2.28−2.19 (m, 1H), 2.2 (d, J = 9.6 Hz, exchangeable SH), 2.05 (d, J = 0.8 Hz, 3H), 2.0−1.83 (m, 2H), 1.81−1.69 (m, 1H), 1.65−1.51 (m, 1H), 1.37 (s, 3H), 0.86 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.3 (C), 140.5 (CH), 139.1 (CH), 125.9 (C), 119.3 (C), 56.6(C), 39.5 (CH), 39.1 (CH_2), 39.0 (CH_3), 29.2 (CH_2), 24.2 (CH_2), 17.4 (CH_3), 15.0 (CH_3), 8.2 (CH_3); IR (KBr) ν 2594, 1701, 1461, 1434, 1146, 1046, 797 cm^{-1}; LRMS (EI) m/z 254 (M^++2, 2), 253 (M^++1, 7), 252 (M^+, 44), 127 (78), 111 (100), 32 (100), 28 (100); HRMS (FAB) m/z calcd for $C_{14}H_{21}O_2S$ $(M + H)^+$ 253.1262, found 253.1255.

(2R,3S)-2,3-Dimethyl-2-((4-methylfuran-3-yl)methyl)-cyclohexanone 2,4,6-Triisopropylbenzenesulfonylhydrazone ***14a.*** To **12** (51 mg, 0.23 mmol) in THF (0.5 mL) and CH_3CN (1 mL) was added 2,4,6-tri-*i*-Pr-benzenesulfonyl hydrazine (0.078 g, 0.26 mmol) and one drop of 48% aqueous HBF_4. The reaction mixture was stirred at rt for 2 h and cooled at 0 °C, solid $NaHCO_3$ (0.04 g, 0.48 mmol) was added, and the volatiles were removed (oil pump) at rt. Column chromatography (95:5 hexane/AcOEt) gave 17 mg of starting material and 50 mg (43%) of **14a** as a white foam. The yield of **14a** in THF at rt for 41 h without acid catalyst was 18% and with TsOH and anhydrous $MgSO_4$ in dry THF (84 h) was 8% (33% recovery of **12**). **14a**: white foam; $[\alpha]^{23}_D$ = −62.0 (c 1.28 in $CHCl_3$); ^{1}H NMR (300 MHz, Z and E isomers) δ 7.3−7.34 (broad signal, exchangeable NH), 7.14 (s, 2H), 6.99−6.96 (m, 1H), 6.47 (s, 1H), 4.2 (h, J = 6.6 Hz, 2H), 2.9 (h, J = 6.6 Hz, 1H), 2.72 (dd, J = 15, 0.9 Hz, 1H), 2.38 (d, J = 15 Hz, 1H), 2.28−2.09 (m, 2H), 1.82 (d, J = 1.2 Hz, 3H), 1.78−1.34 (m, 5H), 1.26 (d, J = 6.6 Hz, 6H), 1.25 (d, J = 6.6 Hz, 6H), 1.22 (d, J = 6.6 Hz, 6H), 1.20 (d, J = 6.6 Hz, 6H), 0.88 (s, 3H), 0.77 (d, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz) δ 162.6 (C), 153.4 (C), 151.1 (2 C), 141.1 (CH), 138.1 (CH), 131.2 (C), 123.7 (2 CH), 120.8 (C), 120.5 (C), 46.7 (C), 37.0 (CH), 34.2 (CH), 30.4 (CH_2), 29.8 (2 CH), 28.8 (CH_2), 24.8 (4 CH_3), 24.6 (4 CH_3), 23.5 (2 CH_3), 23.5 (2 CH_3), 22.8 (CH_2), 22.2 (CH_2), 21.2 (CH_3), 15.9 (CH_3), 8.4 (CH_3); IR (KBr) ν 3300−3100, 1601, 1459, 1384, 1052, 757, 1324, 1158 cm^{-1}; LRMS (EI) m/z 502 (M^++2, 30), 501 (M^++1, 50), 500 (M^+, 42), 405 (26), 267 (57), 251 (57), 233 (100), 203 (57), 109 (58), 95 (61); HRMS (FAB) m/z calcd for $C_{29}H_{45}N_2O_3S$ $(M + H)^+$ 501.3151, found 501.3159.

(2R,3S)-2,3-Dimethyl-2-((4-methylfuran-3-yl)methyl)-cyclohexanone Azine ***14b.*** To **12** (0.04 g, 0.18 mmol) in EtOH (1 mL) were added 2,4,6-tri-*i*-Pr-benzenesulfonyl hydrazine (0.07 g, 0.24 mmol) and HOAc (4 microdrops added with a capillary tube). After the mixture was stirred at rt for 21 h, the solvent was removed in the pump oil and the residue purified by column chromatography (95:5 hexane/AcOEt) to give 23 mg (29%) of azine **14b** as a viscous colorless oil: $[\alpha]^{23}_D$ = −11.3 (c 0.23 in $CHCl_3$); ^{1}H NMR (300 MHz) δ 7.12 (s, 2H), 2.82 (d, J = 14.5 Hz, 1H), 2.66 (d, J = 14.5 Hz, 1H), 2.30−2.21 (m, 2H), 1.96 (d, J = 0.9 Hz, 3H), 1.96−1.36 (3 m, 5 H), 1.06 (s, 3H), 0.92 (d, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz) δ 165.4 (C), 140.8 (CH), 139.5 (CH), 121.7 (C), 121.2 (C), 46.5 (C), 37.9 (CH), 31.0 (CH_2), 29.2 (CH_2), 24.0 (CH_2), 22.6 (CH_2), 21.1 (CH_3), 16.0 (CH_3), 8.6 (CH_3); IR (film) ν 1622, 1459, 1381, 1146, 1051, 873, 788, 757 cm^{-1}; LRMS (EI) m/z 438 (M^++2, 9), 437 (M^++1, 32), 436 (M^+, 69), 341 (39), 220 (63), 219 (30), 218 (100), 217 (76), 203 (54), 95 (100); HRMS (FAB) m/z calcd for $C_{28}H_{41}N_2O_2$ $(M + H)^+$ 437.3168, found 437.3172.

(1R,2R,3S)-1-Hydroxy-2,3-dimethyl-2-((4-methylfuran-3-yl)-methyl)cyclohexanecarbonitrile trimethylsilyl Ether and (1S,2R,3S)-1-Hydroxy-2,3-dimethyl-2-((4-methylfuran-3-yl)methyl)-cyclohexanecarbonitrile Trimethylsilyl Ether ***15a,b.*** To a solution of ketone **12** (0.040 g, 0.18 mmol) in dry C_6H_6 (0.6 mL) was added KCN (0.0027 g, 0.04 mmol), 18-crown-6 ether (0.0068 g, 0.026 mmol) and Me_3SiCN (0.04 mL, 0.03 mmol) under Ar and the mixture stirred for 3 h at rt. The reaction was quenched with brine and the benzene layer separated. The aqueous layer was extracted with CH_2Cl_2 and the combined organic extracts washed with brine, dried (Na_2SO_4) and concentrated at reduced pressure. Column chromatography (95:5 hexane/AcOEt) of the residue (0.07 g) gave a 3:1 mixture of diastereoisomeric protected cyanohydrins (0.055 g, 97%) as a colorless oil. **15a,b**: R_f = 0.70 (9:1, hexane/AcOEt); $[\alpha]^{23}_D$ = +23.6 (c 0.44 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ signals common to both diastereoisomers 2.73 (d, J_{AB} = 15 Hz, H_A), 2.67 (d, J_{AB} = 15 Hz, H_B), 1.92−1.18 (m, 7H); signals of major isomer δ 7.19 (s, 1H), 7.15−7.13 (m, 1H), 2.01 (d, J = 1.2 Hz, 3H), 0.92 (d, J = 6.9 Hz, 3H), 0.91 (s, 3H), 0.20 (s, 9H); signals of minor isomer δ 7.22 (s, CH), 7.17−7.15 (m, 1H), 2.0 (d, J = 1.2 Hz, 3H), 1.06 (s, 3H), 0.85 (d, J = 6.9 Hz, 3H), 0.26 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.1 (CH), 138.8 (CH), 122.0 (C), 121.7 (CN), 121.4 (C), 78.6 (C), 12.3 (CH_3), 8.8 (CH_3); signals for major isomer δ 45.5 (C), 37.2 (CH), 35.3 (CH_2), 30.3 (CH_2), 29.6 (CH_2), 21.8 (CH_2), 16.7 (CH_3), 1.4 (3 CH_3); signals for minor isomer δ 44.5 (C), 35.1 (CH_2), 33.7 (CH), 30.0 (CH_2), 29.8 (CH_2), 19.7 (CH_2), 16.3 (CH_3), 1.3 (3 CH_3); IR (film) ν 1255, 1451, 1134, 1107, 1050, 936, 878, 845, 791, 759 cm^{-1}; LRMS (EI) m/z 320 (M^++1, 4), 319 (M^+, 13), 96 (100), 95 (51), 73 (38); HRMS (FAB) m/z calcd for $C_{18}H_{30}NO_2Si$ $(M + H)^+$ 320.2046, found 320.2048.

Preparation and Separation of Free Cyanohydrins *β*-OH 16a and *α*-OH 16b. Two identical batches of crude protected cyanohydrins **15a,b** (0.28 g) obtained from ketone **12** (0.18 g, 8.1 mmol) were dissolved in THF (14 mL), 10% HCl (4 mL) was added, and the reaction mixture was stirred at rt for 19 h. The volatiles were removed at reduced pressure, diluted with brine, extracted with CH_2Cl_2, dried (Na_2SO_4), and concentrated under reduced pressure to give crude cyanohydrins (0.23 g). The crude material was combined and after column chromatography separation (95:5 hexane/AcOEt) gave the β-OH isomer **16a** (0.25 g, 60% overall from **12**) and the α-OH isomer **16b** (0.12 g, 28% overall from **12**) as crystalline solids.

(1R,2R,3S)-1-Hydroxy-2,3-dimethyl-2-((4-methylfuran-3-yl)-methyl)cyclohexanecarbonitrile (β-OH ***16a*****):** colorless solid; mp 96−98 °C; R_f = 0.56 (85:15, hexane/AcOEt); $[\alpha]^{22}_D$ = +38.6 (c 1.04 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (s, 1H), 7.26−7.24 (m, 1H), 2.90 (s, exchangeable OH), 2.77 (d, J_{AB} = 15 Hz, H_A), 2.71 (d, J_{AB} = 15 Hz, H_B), 2.06 (d, J = 1.2 Hz, 3H), 1.91−1.85 (m, 1H,), 1.85−1.65 (m, 4H), 1.56−1.45 (m, 1H), 1.35−1.23 (m, 1H), 1.05 (s, 3H), 1.0 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.9 (CH), 141.1 (CH), 122.4 (C), 121.8 (CN), 120.3 (C), 77.8 (C), 45.2 (C), 38.9 (CH), 33.9 (CH_2), 32.1 (CH_2), 29.7 (CH_2), 22.2 (CH_2), 16.0 (CH_3), 11.4 (CH_3), 8.8 (CH_3); IR (KBr) ν 3365, 2236, 1452, 1416, 1102, 1051, 1020 cm^{-1}; LRMS (EI) m/z 247 (M^+, 6), 96 (100), 95 (100); HRMS (FAB) m/z calcd for $C_{15}H_{22}NO_2$ $(M + H)^+$ 248.1651, found 248.1647.

(1S,2R,3S)-1-Hydroxy-2,3-dimethyl-2-((4-methylfuran-3-yl)-methyl)cyclohexanecarbonitrile (α-OH ***16b*****):** colorless solid; mp 81 °C; R_f = 0.53 (85:15, hexane/AcOEt); $[\alpha]^{22}_D$ = −9.6 (c 1.35 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (s, 1H), 7.25−7.23 (m, 1H), 2.75 (d, J_{AB} = 16 Hz, H_A), 2.69 (d, J_{AB} = 16 Hz, H_B), 2.64 (d, J = 2 Hz, exchangeable OH), 2.11 (d, J = 1.5 Hz, 3H), 2.12−2.10 (m, 1H),1.96 (ddd, J = 13, 4.5, 2.0 Hz, 1H), 1.93−1.88 (m, 1H), 1.74−1.63 (m, 1H), 1.55−1.49 (m, 2H), 1.39−1.29 (m, 1H), 1.14 (s, 3H), 1.0 (d, J = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.7 (CH), 140.3 (CH), 121.9 (CN), 120.4 (C), 120.1 (C), 76.7 (C), 43.3 (C), 34.4 (CH_2), 30.7 (CH), 30.0 (CH_2), 29.4 (CH_2), 19.4 (CH_2), 18.3 (CH_3), 16.4 (CH_3), 8.44 (CH_3); IR (KBr) ν 3600−3200, 2233, 1464, 1446, 1385, 1174, 1150, 1052, 1031, 998, 790 cm^{-1}; LRMS (EI) m/z 247 (M^+, 6), 96 (100), 95 (100); HRMS (FAB) m/z calcd for $C_{15}H_{21}NO_2$ (M^+) 247.1572, found 247.1583.

(5S,6R)-5,6-Dimethyl-6-((4-methylfuran-3-yl))methyl)cyclohex-1-enecarbonitrile ***17.*** (a) From the β-OH cyanohydrin **16a**: Cyanohydrin **16a** (0.25 g, 1 mmol) in dry pyridine (1.65 mL) was cooled at 0 °C and $POCl_3$ (0.3 mL, 3.25 mmol) was added dropwise. After 30 min at 0 °C, 14 h at rt, and 2 h at 93 °C, the dark brown solution was cooled at 0 °C, poured into ice, and extracted with *t*-BuOMe. The organic layer was washed with saturated $NaHCO_3$, brine, dried (Na_2SO_4), and concentrated under reduced pressure. Column chromatography (2% → 5% AcOEt in hexane) of the crude product (0.26 g) gave the unsaturated nitrile **17** (0.16 g, 70%), saturated ketone (0.015 g, 7%), and recovered starting cyanohydrin (0.031 g, 13%). (b) From the α-OH cyanohydrin **16b**: The same procedure as above was followed with cyanohydrin **16b** (0.1 g, 0.4 mmol), dry pyridine (0.7 mL) and $POCl_3$ (0.12 mL, 1.3 mmol). Column

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chromatography purification of the crude product (0.12 g) gave the unsaturated nitrile **17** (0.029 g, 31%), saturated ketone **12** (0.0065 g, 7%), and recovered starting cyanohydrin (0.044 g, 43%). Unsaturated nitrile **17**: colorless solid; mp 59−60 °C, R_f = 0.56 (85:15, hexane/AcOEt); $[\alpha]^{22}_D$ = −88.3 (*c* 1.33 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (s, 1H), 7.15−7.13 (m, 1H), 6.65 (ddd, *J* = 5.2, 3.2, 0.9 Hz, 1H), 2.71 (d, *J* = 15.2 Hz, 1H), 2.57 (d, *J* = 15.2 Hz, 1H), 2.14 (dtd, *J* = 19.8, 5.4, 3.2 Hz, 1H), 2.08−1.98 (m, 1H), 1.96 (d, *J* = 1.2 Hz, 3H), 1.73−1.63 (m, 1H), 1.63−1.54 (m, 1H), 1.46−1.34 (m, 1H), 1.12 (s, 3H), 0.95 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.2 (CH), 140.8 (CH), 139.0 (CH), 122.1 (C), 120.8 (C), 120.4 (C), 119.0 (CN), 40.8 (C), 32.0 (CH), 31.7 (CH_2), 25.7 (CH_2), 25.5 (CH_2), 21.9 (CH_3), 16.3 (CH_3), 8.5 (CH_3); IR (KBr) ν 2212, 1629, 1457, 1380, 1144, 1047, 871, 792 cm^{-1}; LRMS (EI) *m*/*z* 230 (M^++1, 5), 229 (M^+, 28), 96 (32), 95 (100); HRMS (FAB) *m*/*z* calcd for $C_{15}H_{20}NO$ $(M + H)^+$ 230.1545, found 230.1549.

(5S,6R)-5,6-Dimethyl-6-((4-methylfuran-3-yl)methyl)cyclohex-1-enecarboxylic Acid ***18a***. The unsaturated nitrile **17** (0.074 g, 0.32 mmol) and KOH (0.8 g, 14 mmol) in ethylene glycol (3.4 mL) were heated at 180 °C (silicone oil bath) under Ar for 24 h. It was cooled in an ice bath, water was added and extracted with *t*-BuOMe. The organic layer was washed with brine, dried (Na_2SO_4), and concentrated at reduced pressure to give 0.044 g (the "neutral" fraction). The aqueous layer was cooled in an ice bath, acidified (pH∼1) with 18% HCl, extracted with AcOEt, washed with brine, dried (Na_2SO_4) and concentrated at reduced pressure. Column chromatography (8:2 hexane/Me_2CO) of the residue (0.1 g) afforded acid **18a** (0.05 g, 63%). An additional amount of acid (0.006g, 7%), recovered nitrile (0.0024 g, 6%) and traces of the intermediate amide were obtained by column chromatography (98:2 hexane/AcOEt→8:2 hexane/Me_2CO) of the "neutral fraction". Acid **18a**: viscous oil, R_f = 0.51 (7:3, hexane/Me_2CO); $[\alpha]^{22}_D$ = −20.8 (*c* 1.49 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 13−10 (brs, exchangeable CO_2H), 7.19 (dd, 1 H, *J* = 4.8, 3.2 Hz, 1H), 7.12−7.09 (m, 1H), 7.06 (s, 1H), 3.13 (d, J_{AB} = 15.2 Hz, H_A), 2.58 (d, J_{AB} = 15.2 Hz, H_B), 2.27−2.03 (m, 2H), 1.93 (d, *J* = 0.8 Hz, 3H), 1.81−1.69 (m, 1H), 1.61−1.51 (m, 1H), 1.50−1.35 (m, 1H), 1.21 (s, 3H), 0.93 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173 (C), 144.7 (CH), 140.2 (CH), 138.6 (CH), 136.4 (C), 121.8 (C), 121.0 (C), 40.3 (C), 33.7 (CH), 29.8 (CH_2), 25.8 (CH_2), 25.6 (CH_2), 21.1 (CH_3), 15.9 (CH_3), 8.4 (CH_3); IR (film) ν 3500−2300, 1682, 1627, 1455, 1411, 1384, 1264, 1236, 1148, 1053, 940, 874, 792, 759 cm^{-1}; LRMS (EI) *m*/*z* 250 (M^++2, 2), 249 (M^++1, 13), 248 (M^+, 19), 153 (77), 152 (62), 107 (100), 96 (79), 95 (47); HRMS (FAB) *m*/*z* calcd for $C_{15}H_{20}O_3$ (M^+) 248.1412, found 248.1406.

Methyl (5S,6R)-5,6-Dimethyl-6-((4-methylfuran-3-yl)methyl)-cyclohex-1-enecarboxylate ***18b***. Crude acid **18a** (0.046 g) in Me_2CO (1 mL) was cooled at 0 °C, and excess ethereal solution of CH_2N_2 was added. After 1 h at rt, the volatiles were removed at reduced pressure and the residue purified by column chromatography (98:2 hexane/AcOEt) to give methyl ester **18b** (0.02 g, 41% overall yield from **17**). **18b**: colorless oil; R_f = 0.59 (9:1, hexane/Me_2CO); $[\alpha]^{22}_D$ = −12.6 (*c* 1.16 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.11−7.10 (m, 1H), 6.97−6.95 (m, 1H), 6.96 (dd, *J* = 5, 3 Hz, 1H), 3.70 (s, 3H), 3.06 (dd, *J* = 15, 1.0 Hz, 1H), 2.59 (d, *J* = 15 Hz, 1H), 2.2−2.12 (m, 1H), 2.12−2.03 (m, 1H), 1.93 (dd, *J* = 1, 0.5 Hz, 3H), 1.79−1.7 (m, 1H), 1.59−1.53 (m, 1H), 1.47−1.38 (m, 1H), 1.21 (s, 3H), 0.92 (d, *J* = 6.5, 3H); ^{13}C NMR (125 MHz) δ 167.9 (C), 141.4 (CH), 140.2 (CH), 138.6 (CH), 137.3 (C), 121.9 (C), 121.1 (C), 51.3 (CH_3), 40.5 (C), 33.6 (CH), 30.0 (CH_2), 25.9 (CH_2), 25.3 (CH_2), 21.3 (CH_3), 16.0 (CH_3), 8.4 (CH_3); IR (film) ν 1712, 1633, 1455, 1434, 1251, 1225, 1088, 1052, 1034, 790, 760 cm^{-1}; LRMS (EI) *m*/*z* 264 (M^++2, 4), 263 (M^++1, 13), 262 (M^+, 13), 231 (33), 167 (45), 166 (48), 135 (74), 107 (100), 96 (24); HRMS (FAB) *m*/*z* calcd for $C_{16}H_{22}O_3$ M^+ 262.1569, found 262.1574.

(5S,6R)-5,6-Dimethyl-6-((4-methyl-3-furan-3-yl)methyl)cyclohex-1-enecarbaldehyde ***19***. Compound **17** (0.056 g, 0.24 mmol) in dry toluene (4 mL) was cooled at 0 °C and under Ar was added a 1.5 M solution of DIBALH in toluene (0.5 mL, 0.75 mmol). After the mixture was stirred for 3 h, water (1 mL) was added, the mixture stirred for 90 min to reach rt and filtered through a pad of Celite, and the cake thoroughly washed with Et_2O. The filtrate was washed with brine, dried (Na_2SO_4), and concentrated to give 0.06 g of crude product. Column chromatography (98:2 hexane/AcOEt) afforded pure **19** (0.021 g, 36%) as a white solid. Purification by column chromatography (Et_2O) with basic Al_2O_3 gave an 85% yield recovery of impure **19** which was used in the oxidation experiments.

19: unstable white solid; R_f = 0.60 (85:15 hexane/AcOEt); $[\alpha]^{20}_D$ = −8.0 (*c* 1.24 in $CHCl_3$); ^{1}H NMR (300 MHz) δ 9.39 (s, 1H), 7.10−7.70 (m, 1H), 6.92 (s, 1H), 6.81 (dd, *J* = 4.7, 3 Hz, 1H), 3.27 (d, *J* = 15.3 Hz, 1H), 2.53 (d, *J* = 15.3 Hz, 1H), 2.34 (m, 1H), 2.21 (m, 1H), 1.92 (d, *J* = 0.9 Hz, 3H), 1.79−1.67 (m, 1H), 1.64−1.54 (m, 1H), 1.48−1.33 (m, 1H), 1.15 (s, 3H), 0.94 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (100 MHz) δ 195.2 (C), 155.6 (CH), 147.2 (C), 140.0 (CH), 138.7 (CH), 122.0 (C), 121.1 (C), 40.2 (C), 33.4 (CH), 28.7 (CH_2), 26.6 (CH_2), 26.0 (CH_2), 20.2 (CH_3), 15.5 (CH_3), 8.5 (CH_3); IR (KBr)ν 1686, 1629, 1457, 1376, 1178, 1149, 1052, 869, 793 cm^{-1}; LRMS (EI) *m*/*z* 234 (M^++2, 4), 233 (M^++1, 25), 232 (M^+, 82), 203 (31), 137 (87), 136 (63), 109 (87), 96 (71), 95 (100); HRMS (FAB) calcd for $C_{15}H_{20}O_2$ (M^+) 232.1463, found 232.1465.

(+)-9-Oxoeuryopsin ***1***. Acid **18a** (0.03 g, 0.12 mmol) in dry C_6H_6 (1.6 mL) was cooled at 5 °C and under Ar was added PCl_5 (0.028g, 0.12 mmol). The green solution was stirred at 5 °C for 25 min and at rt for 1 h. It was cooled at 5 °C, and $SnCl_4$ (0.03 mL, 0.25 mmol) was added (0.1 mL C_6H_6 for rinsing). After 30 min, the red solution was quenched with ice and 18% HCl (1 mL) and extracted with *t*-BuOMe. The combined organic extracts were washed with 1 N HCl (2 mL), water (2 mL), 5% Na_2CO_3 (3 × 2 mL), and brine (2 × 2 mL) and dried (Na_2SO_4). After removal of solvent at reduced pressure the yellow oily residue (0.030 g) was purified by column chromatography (10% → 15% → 20% AcOEt in hexane) to afford synthetic (+)-9-oxoeuryopsin as a white solid (0.016 g, 59%). **1**: mp 124−125 °C; R_f = 0.54 (7:3, hexane/AcOEt); $[\alpha]^{20}_{589}$ = +6.5, $[\alpha]^{20}_{578}$ = +8.7, $[\alpha]^{20}_{546}$ = +16.9, $[\alpha]^{20}_{436}$ = +158.5 (*c* 1.3 in $CDCl_3$) ; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42−7.41 (m, 1H), 6.99 (t, *J* = 4 Hz, 1H), 2.80 (d, J_{AB} = 16.5 Hz, H_A), 2.48 (d, J_{AB} = 16.5 Hz, H_B), 2.32−2.26 (m, 2H), 2.0 (d, *J* = 1.5 Hz, 3H), 1.87−1.78 (m, 1H), 1.63−1.46 (m, 2H), 1.05 (d, *J* = 7 Hz, 3H), 1.02 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.9 (C), 147.0 (C), 145.2 (CH), 142.5 (C), 137.3 (C), 136.6 (CH), 121.3 (C), 40.4 (C), 40.0 (CH), 34.2 (CH_2), 26.3 (CH_2), 26.1 (CH_2), 20.5 (CH_3), 15.6 (CH_3), 7.7 (CH_3); UV (λ_{max}, Et_2O) 291 nm (ε 24882), UV (λ_{max}, MeOH) 304 nm (ε 25898); IR (CCl_4) ν 1674, 1626, 1607, 1537, 1461, 1420, 1347, 908, 874 cm^{-1}; LRMS (EI) *m*/*z* 232 (M^++2, 6), 231 (M^+ + 1, 33), 230 (M^+, 100); HRMS *m*/*z* calcd for $C_{15}H_{19}O_2$ $(M + H)^+$ 231.1385, found 231.1388.

Lit.:[7] colorless crystals; mp 119−120 °C; $[\alpha]_{589}$ = +0.35, $[\alpha]_{578}$ = +2.8, $[\alpha]_{546}$ = +7.1, $[\alpha]_{436}$ = +9.65 (*c* 1.3 in $CDCl_3$); ^{1}H NMR (100 MHz, $CDCl_3$) δ 7.31 (c, *J* = 1 Hz, 1H), 6.77 (t, *J* = 3.9 Hz, 1H), 2.74 (d, J_{AB} = 16 Hz, H_A), 2.38 (d, J_{AB} = 16 Hz, H_B), 1.98 (d, *J* = 1 Hz, 3H), 2.23 (m, 2H), 1.03 (s, 3H), 0.98 (s, 3H); UV λ_{max} 291 nm (ε 16200); IR (CCl_4) ν 1675, 1625, 1605, 1540, 830 cm^{-1}; MS (EI) *m*/*z* calcd for $C_{15}H_{18}O_2$ $(M + H)^+$ 230.130, found 230.130, 215 (38), 202 (9), 188 (13), 173 (12), 159 (5).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of ^{1}H and ^{13}C NMR spectra of all compounds, crystal data for compounds **1**, *anti*-**10**, **12**, and **16a**, and experimental and simulated ECD curves for **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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