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Enantioselective Total Synthesis of the Mexicanolides: Khayasin, Proceranolide, and Mexicanolide

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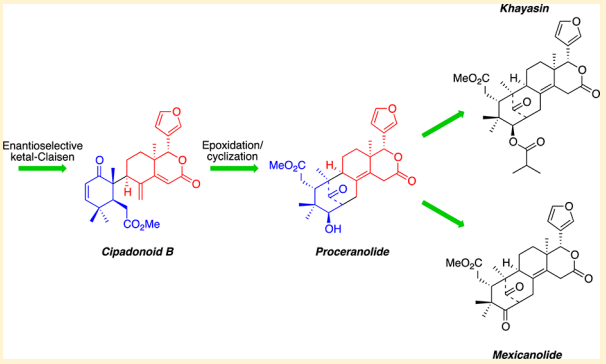
Supporting Information

ABSTRACT: The enantioselective total synthesis of the limonoids khayasin, proceranolide and mexicanolide was achieved via a convergent strategy utilizing a tactic aimed at incorporating natural products as advanced intermediates. This extended biomimetically inspired approach additionally achieved the enantioselective total synthesis of the intermediates azedaralide and cipadonoid B.

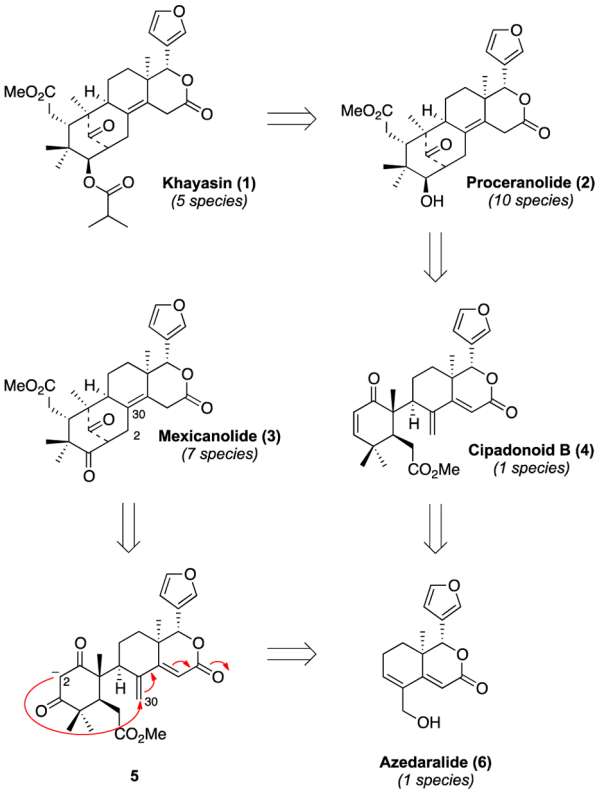


INTRODUCTION

The tetranortriterpenoid khayasin (**1**) (Scheme 1), which was isolated in 1966 by Taylor,[1] belongs to the mexicanolide class of limonoid natural products, also known as the bicyclononanolides.[2] More importantly, however, khayasin (**1**) recently surfaced as a potent and selective insecticide[3−5] against the devastating Coconut leaf beetle *Brontispa longissima*.[6,7]

Beyond the biological implications, the attraction to this group of natural products came from the contemplated retrosynthetic analysis, which stemmed from a potentially extended biogenetic relationship most likely existing between limonoids isolated from both the meliaceae and rutaceae.[8−10] Further clues on this front have been provided by Connolly, who proposed a biosynthetic route to mexicanolide (**3**)[11,12] via the tentative existence of diketone **5** ultimately arising from a 1,6-conjugate addition involving C-2 and C-30 (Scheme 1). Moreover, the closely delineated structural features of khayasin (**1**) are present across four key natural product intermediates, i.e., proceranolide (**2**),[13−15] cipadonoid B (**4**),[16] and azedaralide (**6**),[17] all of which were isolated from different species (Scheme 1) within the meliaceae. Thus, our recent racemic synthesis[18] of cipadonoid B (**4**), derived from azedaralide (**6**), could provide the foundation for potential access to a range of mexicanolide natural products. Successful completion of some mexicanolide examples are now reported herein.

Scheme 1. Khayasin (1) and Key Natural Product Retrosynthetic Intermediates



RESULTS AND DISCUSSION

To initiate this study, a synthesis of azedaralide (**6**) was required. Previous work from our group in this area[19] had demonstrated that racemic (±)-azedaralide (**6**)[20,21] can be

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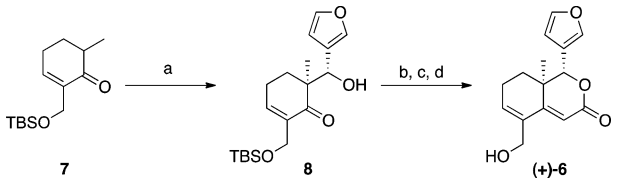
constructed in eight steps in 14% yield starting from 2-cyclohexenone. However, an enantioselective synthesis was critical, not only from a biological perspective but also for absolute stereochemical confirmation of the downstream targets. In approaching an azedaralide (**6**) enantioselective synthesis, the key diastereoselective aldol reaction (i.e., **7** to **8**, Scheme 2) seemed the obvious point for installing asymmetry, but there were limited enantioselective options for an aldol reaction of this nature.

Scheme 2[a]



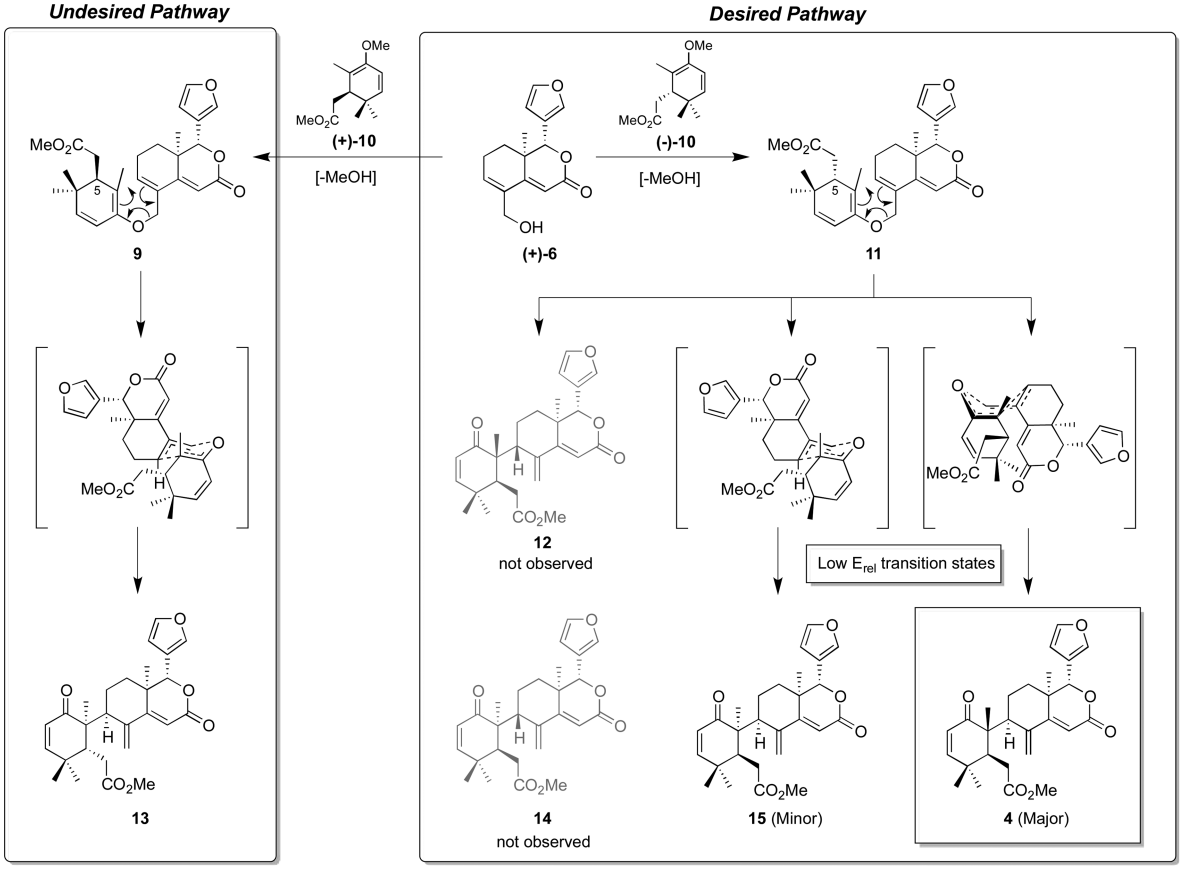
[a]Key: (a) (i) KHMDS, THF, −78 °C, then (−)-DIP-Cl, (ii) 3-furylaldehyde, 33−44%, 80−90% ee; (b) Ac_2O, DMAP, pyridine 57%; (c) LDA, THF, −78 °C, then rt, 39%; (d) TBAF, THF, −20 °C, 97%.

Unfortunately, the lead methodology using (*S*)-(−)-1-amino-2-methoxymethylpyrrolidine (SAMP)[22,23] failed to be applicable to **7**. Nevertheless, the chiral borane (−)-diisopinocampheyl chloroborane [(−)-DIP-Cl][24] gave product (+)-**8** using a modification[25] of the original procedure in 80−90% ee.[26] Alcohol **8** could then be taken through to the required (+)-azedaralide (**6**) in three steps with no loss in enantiomeric purity (Scheme 2). The opposite enantiomer [(−)-azedaralide] could also be obtained, if (+)-DIP-Cl was used.

With both enantiomers of azedaralide in hand, these could now be applied to either synthesis of (+)- or (−)-cipadonoid B (**4**). The known, but rarely applied, ketal−Claisen rearrangement[27−35] used in the synthesis of racemic (±)-cipadonoid B (**4**) (Scheme 3),[18] however, was poorly understood in terms of stereochemical outcome. In brief, when this reaction was performed in the racemic series it produced undesired diastereoisomers (i.e., **13** and **15**) of the natural product cipadonoid B (**4**). We believed this was due to the reaction between matched enantiomers of racemic azedaralide (**6**) and the racemic starting enol ether **10** leading down desired and undesired pathways. Furthermore, we surmised that a combination of low energy barrier boat and chair transition states were giving rise to further selectivity in the desired pathway. That is, it precludes diastereoisomers **12** and **14** but leads to cipadonoid B (**4**) and a second diastereoisomer (**15**) driven by the methylene ester at position 5 of the exchanged enol ether (**11**) (Scheme 3). If this hypothesis were to be proven correct this would open the possibility to introduce asymmetry into the desired pathway, which would in addition prevent access to the undesired pathway.

To gain evidence for our mechanistic theory, a computational investigation of the reaction pathway using each individual enantiomer in the desired and undesired case was undertaken using Gaussian09[36] (M05-2X,[37] 6-311+G(d,p),[38,39] C-

Scheme 3[a]



[a]Conditions: $TsOH_{(cat)}$, xylenes, 180 °C, 4 h.

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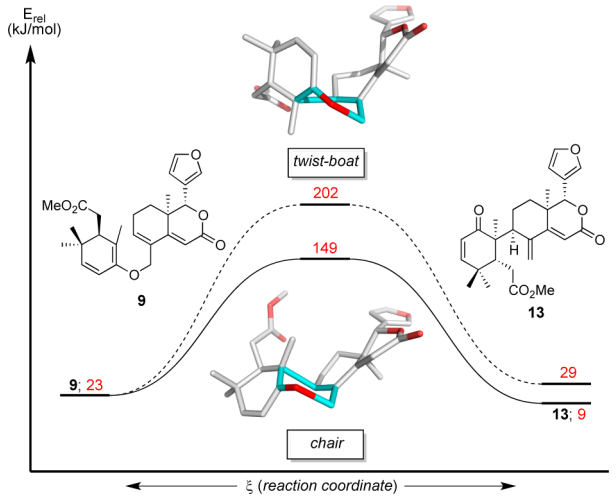


Figure 1. Energy levels of the Claisen rearrangement of **9** with the two lower energy transition states and corresponding products.

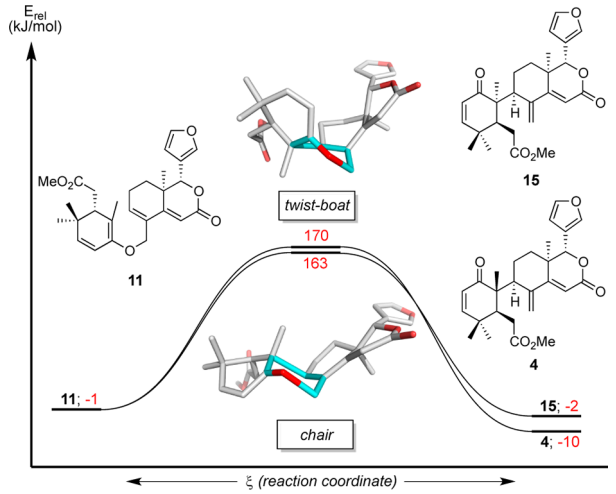


Figure 2. Energy levels of the Claisen rearrangement of **11** with the two lower energy transition states and corresponding products.

PCM,[40−42] in xylene, Supporting Information) (Figures 1 and 2). This key, one-pot transformation, between methyl vinyl ether **10** and azedaralide (**6**) first undergoes ether exchange to give the enol ether intermediates **9** and **11** with ground-state energy levels of 23 and −1 kJ/mol, respectively (relative to **6** and **10**). The Claisen rearrangement ensues, producing just three (**4**, **13**, and **15**) of a possible eight diastereoisomers (Scheme 3). Modeling all possible transition states along with starting materials (**9** and **11**), and product ground states, revealed that only three diastereoisomers were energetically favored (**4**, **13**, and **15**) (Figures 1 and 2), which corresponded exactly with the experimental outcome. That is, diastereoisomers **13** and **15** arise via chair transition states, whereas cipadonoid B (**4**) is obtained via a twist-boat transition state. The remaining diastereoisomers arising from **9** (not shown) and **11** (**12** and **14**) are not energetically favored and as such were not observed. In essence, as predicted, the course of reaction is controlled by avoiding a large (>300 kJ/mol) steric interaction created by the C-5 methylene ester stereocenter contained within **9** and **11** (Scheme 3). Finally, even though Scheme 3 indicates a nonreversible process, the calculations supported our observations that the Claisen reaction was indeed in thermodynamic equilibrium. To illustrate this further, comparison of the ground-state energies of both starting enol ether **11** and products, (±)-cipadonoid B (**4**) and the diastereoisomer (**15**), show energy differences of 9 and 1 kJ/mol, respectively, and only a minor difference (7 kJ/mol) in activation energies indicating the potential for reversibility under the energetic reaction conditions.

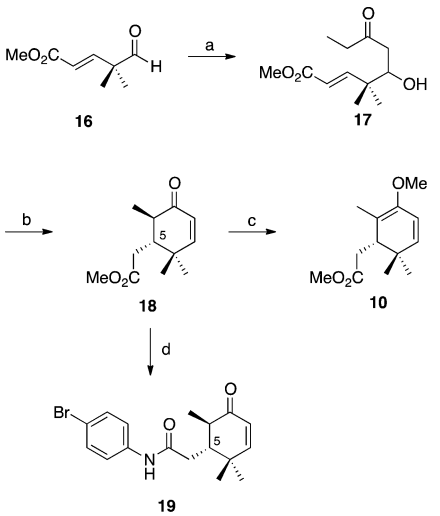
Now presented with a clearer understanding of the process, the second issue of cipadonoid B (**4**) yield optimization could be potentially resolved if diastereoisomer **13**, generated from enol ether **9** and constituting a significant portion of product distribution, was eliminated from the process. This was very achievable if a single enantiomer of enol ether **11** could be accessed from matched single enantiomers of both azedaralide (**6**) and the methyl vinyl ether **10** (Scheme 3).

By serendipity the enantioselective synthesis of vinyl ether **10** was also achieved using an enantioselective aldol reaction mediated by (+)-DIP-Cl, but not before demonstrating that attempts using proline catalysis,[43] tryptophan-derived oxazaborolidine catalyst,[44,45] and BINOL-derived titanium dichloride[46] were all unsuccessful.

After some optimization,[47] the key aldol reaction involving aldehyde **16** gave hydroxy ketone **17** in 47% yield and 92.5% ee. Even though we were unable to confirm the configuration of **17** at C5, it underwent base-promoted cyclization, with no loss in asymmetric induction, giving cyclohexenone **18** as a 4:1 mixture of diastereoisomers (epimeric at C6), both with the desired stereochemistry at C-5. COMU-mediated amide coupling[48] with 4-bromoaniline gave **19** as suitable crystals for X-ray analysis that confirmed the absolute stereochemistry (Scheme 4).

The stereochemical outcome of this reaction (i.e., **17** to **18**, Scheme 5) is likely controlled by the specific conformation of a six-membered ring transition state, in which the hydroxy group (or OK group, if fully deprotonated) would adopt a pseudo axial orientation (i.e., **A** or **C**) to prevent a large pseudo $A^{1,3}$-steric interaction with the pendant methylene ester side chain

Scheme 4[a]



[a]Conditions: (a) (i) (+)-DIP-Cl, DIPEA, 2-butanone, Et_2O, −78 °C, (ii) **16**, −105 to −30 °C, 16 h, 47%, 92.5% ee; (b) KH, toluene, 0 °C to rt, 45 min, 69%, 90% ee; (c) MeOTf, 2,6-di-*tert*-butyl-4-methylpyridine, CH_2Cl_2, 90 °C, 4 h, 71%; (d) (i) LiOH, MeOH, (ii) *p*-bromoaniline, COMU, DIPEA, DMF, 0 °C, 83%.

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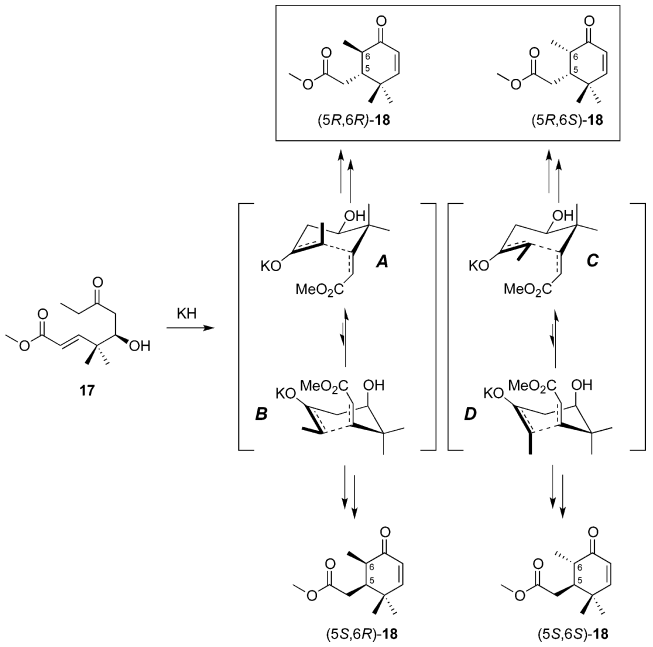
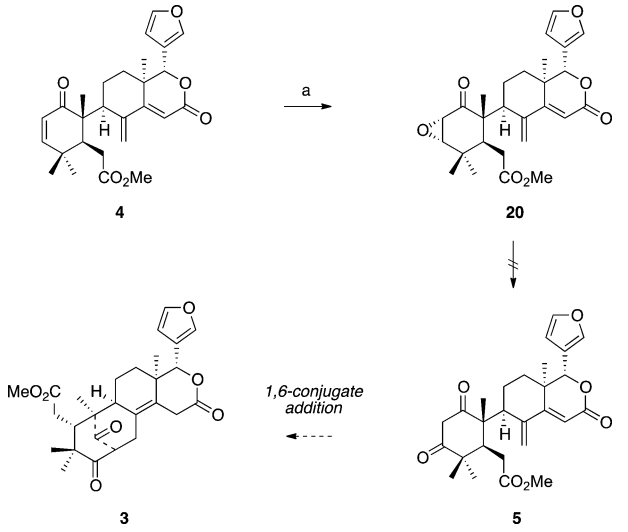
Scheme 5



Scheme 6[a]



[a]Conditions: (a) 30% H_2O_2, K_2CO_3, MeOH, 0 °C to rt, 12 h, 75%.

(i.e., **B** and **D**). The orientation of the C-6 methyl group has little effect on the stereochemical outcome whereas the absolute configuration of C-5 is conserved in both diastereoisomers (Scheme 5). Subsequent elimination of potassium hydroxide (or K_2O) completes the formation of both (5*R*,6*R*)-**18** and (5*R*,6*S*)-**18**.

Lastly, conversion of both (5*R*,6*R*)-**18** and (5*R*,6*S*)-**18** into the desired (−)-vinyl ether **10** was simply achieved using methyl triflate (Scheme 4).

Gratifyingly, subjecting single enantiomers of both (+)-azedaralide[49] (**4**) and vinyl ether (−)-**10** to the ketal−Claisen cascade produced, as predicted, enantiopure (−)-cipadonoid B (**6**) and the minor diastereoisomer **15** in a ratio of 7:3 with >99% ee. The diastereoisomer **13** was also observed in trace amounts, arising from the minor enantiomeric impurity of (+)-vinyl ether **10**.

The optical rotation of (−)-cipadonoid B (**4**) matched the naturally occurring material exactly, confirming the absolute stereochemistry as (5*S*,9*S*,10*R*,13*R*,17*R*).

The focus then shifted to mexicanolide (**3**), with a view to implement an intramolecular 1,6-conjugate addition, which would transform (−)-cipadonoid B (**4**) into mexicanolide (**3**). Toward this strategy (−)-cipadonoid B (**4**) was regio- and stereoselectively epoxidized to introduce β oxygenation at C-3, giving **20** as a single enantiomer (Scheme 6), which unfortunately could not be converted into Connolly's intermediate (**5**). The epoxide **20** was crystallized for X-ray structure analysis, whereby the absolute stereochemistry was confirmed using the Flack parameter.[50] Fortunately, the C-3 stereochemistry was as required for proceranolide (**2**). This tactical maneuver opened options for facilitating reductive and/or single-electron epoxide ring-opening that could lead to (−)-proceranolide (**2**) from either an intermediate carbanion, or radical, driving the desired 1,6-conjugate addition. Unfortunately however, modern procedures (e.g., SmI_2,[51] PhSeNa,[52] Bu_3SnH[53]) returned starting material or promoted decomposition.

Conversely, the rarely encountered reagent, aluminum amalgam,[54,55] was found to fortuitously promote a one-pot cascade initiated by epoxide ring-opening (i.e., **22**) and followed by a 6-*endo*-*trig* cyclization (i.e., **24**) to give (−)-proceranolide (**2**) in 30% yield. Although the yield was on the moderate side, this outcome was more than acceptable considering two difficult transformations were occurring in the one pot. Countless attempts to optimize this sequence, and obtain better control over what appeared to be a promiscuous radical (i.e., **21**) giving rise to byproduct such as **23**, failed to increase the yield, although ultrasonication was found to increase reaction rate.

Further structure confirmation of (−)-proceranolide (**2**) was provided by conversion to (−)-mexicanolide (**3**) using Jones reagent, which was identical in all respects to an authentic sample from *Cedrela odorata*. To complete the synthesis of (−)-khayasin (**1**), acylation of (−)-proceranolide (**2**) was required. Although not straightforward, this last rudimentary transformation proceeded in 71% yield when treated with isobutyric acid and the coupling reagent 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDCI) (Scheme 7).

CONCLUSIONS

We have presented herein the first enantioselective total syntheses of the natural products (+)-azedaralide (**6**), (−)-cipadonoid B (**4**), (−)-proceranolide (**2**), (−)-mexicanolide (**3**), and (−)-khayasin (**1**) using as the key step a ketal−Claisen rearrangement. Interestingly, the ketal−Claisen precursors (i.e., **6** and **10**) were both obtained from DIP-Cl-controlled asymmetric aldol reactions, where other asymmetric aldol protocols failed. From a philosophical viewpoint, however, the applied synthetic strategy, which utilized natural products as the advanced intermediates, possibly broadens the scope of the biomimetic synthesis definition as our approach linked not only species-related but distant genera-related natural products. Furthermore, the series of total syntheses disclosed herein has analogy to the term "collective total synthesis",[56] defined as "the preparation of an intermediate [i.e azedaralide (*Melia azedarach*)] endowed with functionality amenable to the preparation of structurally diverse natural products in different

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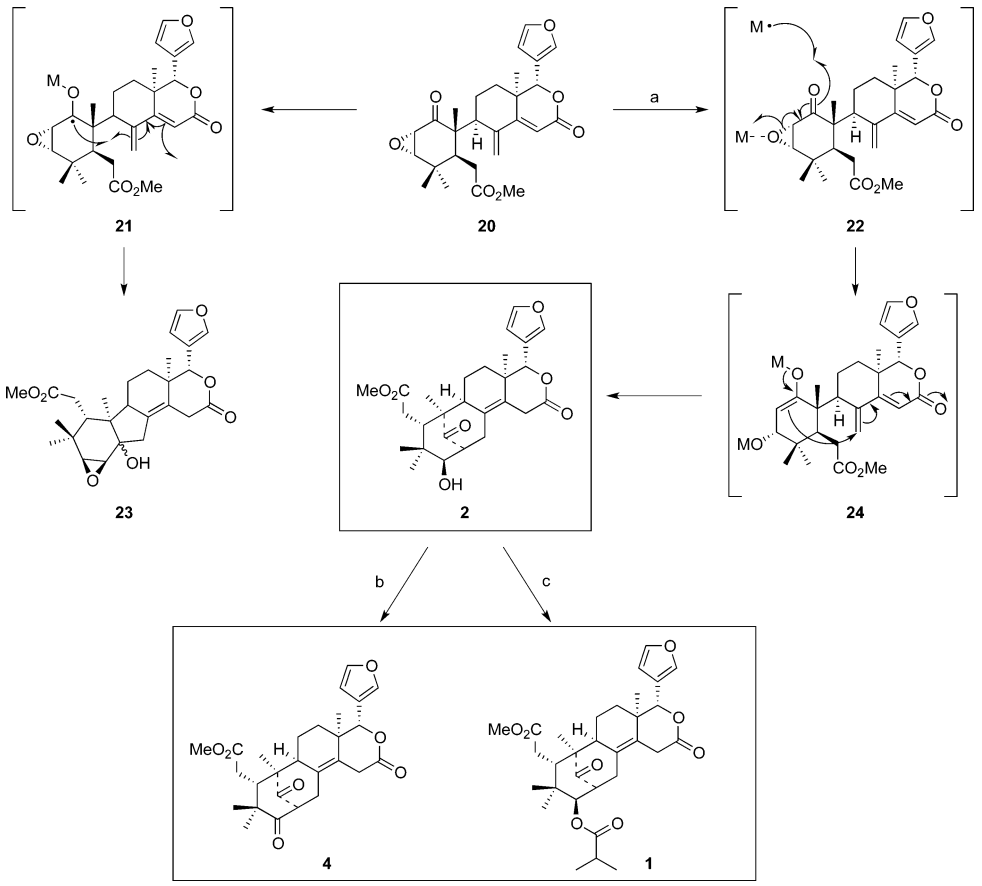
Scheme 7[a]



[a]Conditions: (a) Al/Hg, EtOH/THF/H_2O/$NaHCO_3$, rt,))), 1 h, 30%; (b) $K_2Cr_2O_7$/H_2SO_4, Me_2CO, rt, 15 min, 68%; (c) isobutyric acid, EDCI, DMAP, CH_2Cl_2, 0 °C to rt, 4 h, 71%.

families [e.g. cipadonoid B (*Cipadessa cinerascens*) and proceranolide (*Cedrela odorata*)].

EXPERIMENTAL SECTION

General Methods. All reactions were performed under an atmosphere of argon in oven-dried glassware. Anhydrous solvents for reactions were distilled from sodium (THF, diethyl ether) or CaH_2 (CH_2Cl_2) and used immediately. Column chromatography was performed on silica gel with 40−63 μm particle size, using distilled solvents. Thin-layer chromatography (TLC) was performed on aluminum-backed silica gel plates and visualized either under UV light or using an oxidizing staining solution followed by heating. NMR spectra were recorded at 300, 400, or 500 MHz (^{1}H) and 75, 100, or 125 MHz (^{13}C). Chemical shifts were determined relative to the residual solvent peak: 7.24 ppm (^{1}H), 77.0 ppm (^{13}C). Gas chromatography/mass spectrometry for low-resolution mass determination used electron impact ionization. Positive-mode electrospray ionization (ESI) was used for both low and high-resolution mass detection. High resolution electrospray ionization (HRMS) was performed using a quadrupole-time of flight instrument.

*(S,S)-2-[(tert-Butyldimethylsilyloxy)methyl]-6-[(furan-3-yl)-hydroxymethyl]-6-methyl-2-cyclohexenone (**8**).* To a solution of (+)-α-pinene (ee = 86.5%) (0.639 mL, 4 mmol) in anhydrous THF (1.15 mL) at −10 °C was added chloroborane methyl sulfide complex (0.199 mL, 1.9 mmol) dropwise. The solution was slowly warmed to room temperature and stirred overnight to give a 1 M solution of (+)-DIP-Cl. To the cyclohexenone (**7**) (0.231 g, 0.9 mmol) in THF (1.8 mL) at −78 °C was added KHMDS (0.5 M/toluene) (2.6 mL, 1.3 mmol) dropwise over 10 min. The reaction mixture was stirred for 20 min at this temperature, followed by dropwise addition of the aforementioned (+)-DIP-Cl solution, over 5 min. The resultant mixture was stirred for 1 h, followed by addition of freshly distilled 3-furaldehyde (0.4 mL, 4.6 mmol) dropwise. The reaction mixture was then stirred at −78 °C until complete disappearance of the starting material. It was quenched by the addition of saturated $NaHCO_3$ (10 mL) and extracted with CH_2Cl_2 (4 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried over Na_2SO_4, and concentrated in vacuo to give an oil. Column chromatography (1:5 diethyl ether/petroleum spirit) of the oil gave the titled compound (−)-**8** as a colorless oil (0.14 g, 44%). $[\alpha]_D^{25}$ −44.9 (*c* 2.23, $CHCl_3$). Enantiomeric excess: 90%; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.36 (s, 1H), 7.35 (d, *J* = 1.5 Hz, 1H), 6.97 (br s, 1H), 6.36 (s, 1H), 4.89 (s, 1H), 4.25−4.39 (m, 2H), 2.37−2.41 (br m, 2H), 1.69−1.75 (m, 1H), 1.49−1.53 (m, 1H), 1.17 (s, 3H), 0.90 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 206.2, 144.1, 142.5, 140.5, 136.6, 123.9, 110.1, 71.5, 60.1, 47.5, 31.1, 25.9, 22.3, 18.3, 14.5, 5.5;

Procedure repeated substituting with (−)-α-pinene (ee = 87%) to give (*S,S*)-**8**: $[\alpha]_D^{24}$ +35.6 (*c* 2.20, $CHCl_3$); enantiomeric excess 80%.

*(+)-Azedaralide (**6**).* Acetic anhydride (700 μL, 7.4 mmol, 12 equiv) was added dropwise to a cold (0 °C) and stirring solution of *S,S*-(**8**) (ee = 80%) (221 mg, 0.63 mmol, 1.0 equiv) in pyridine (9.79 μL, 8.7 mmol, 14 equiv) under an argon atmosphere. The cold bath was removed, and *N,N*-dimethylaminopyridine (8 mg, 0.07 mmol, 0.1 equiv) was added. The reaction was stirred at room temperature for 3 h before being quenched with ice−water (5 mL). The mixture was extracted with CH_2Cl_2 (4 × 5 mL), and the combined organic layers were then washed with 2 M HCl and saturated $NaHCO_3$, dried over $MgSO_4$, and evaporated. The residue was purified by column chromatography (3:1 petroleum spirit/diethyl ether) and (*S,S*)-2-[(*tert*-butyldimethylsilyloxy)methyl]-6-[(furan-3-yl)acetoxymethyl]-6-

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methyl-2-cyclohexenone was obtained as a clear, slightly yellow oil (141 mg, 57%).

To a stirred solution of *N*, *N*-diisopropylamine (76 μL, 0.54 mmol) in anhydrous THF (2.5 mL) at 0 °C under an argon atmosphere, was added *n*-butyl lithium (2.38 M in heptane, 192 μL, 0.46 mmol) dropwise. After 30 min at 0 °C, the solution was cooled to −78 °C, and a solution of (*S*,*S*)-2-[(*tert*-butyldimethylsilyloxy)methyl]-6-[(furan-3-yl)acetoxymethyl]-6-methyl-2-cyclohexenone from above (141 mg, 0.36 mmol) in THF (2.5 mL) was added dropwise over 10 min. The reaction was stirred at −78 °C for 5 h, slowly allowed to warm to room temperature, and stirred overnight. The reaction was quenched with saturated NH_4Cl solution (1 mL) and the mixture extracted with CH_2Cl_2 (4 × 1.5 mL) and then washed successively with water and brine. The extracts were then dried over $MgSO_4$, evaporated, and subjected to column chromatography (2:1 petroleum spirit/diethyl ether) to give (*R*,*R*)-5-[(*tert*-butyldimethylsilyloxy)-methyl]-1-(furan-3-yl)-8a-methyl-8,8a-dihydro-1*H*-isochromen-3(7*H*)-one as a colorless oil (52 mg, 39%): $[\alpha]^{28}_D$ +211.3 (*c* 5.24, $CDCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 0.07 (s, 6H), 0.90 (s, 9H), 1.01 (s, 3H), 1.41−1.50 (m, 2H), 2.28−2.37 (m, 2H), 4.30 (ABq, *J* = 1.8, 14.0 Hz, 2H), 5.11 (s, 1H), 5.79 (s, 1H), 6.43 (br s, 2H), 7.40 (d, J1/41.5 Hz, 1H), 7.46 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = −5.38, −5.35, 15.9, 18.3, 22.0, 25.9, 29.9, 37.1, 62.4, 80.7, 109.3, 110.1, 120.2, 132.2, 134.7, 141.1, 142.9, 157.3, 165.8.

Tetrabutylammonium fluoride (1 M in THF, 170 μL, 0.17 mmol) was added dropwise to a −20 °C solution of (*R*,*R*)-5-[(*tert*-butyldimethylsilyloxy)methyl]-1-(furan-3-yl)-8a-methyl-8,8a-dihydro-1*H*-isochromen-3(7*H*)-one from above (52 mg, 0.14 mmol) in THF (1.3 mL). The solution was stirred at this temperature for 2 h, before dilution with ethyl acetate (1 mL) and 1 M hydrochloric acid (1 mL). The reaction mixture was extracted with ethyl acetate (3 × 3 mL), and the combined organic phases washed with brine (4 mL), dried over Na_2SO_4, and concentrated in vacuo. Column chromatography of the residue (diethyl ether) furnished (*R*,*R*)-(+)-azedaralide (**6**) as a cream-colored solid (35 mg, 97%): $[\alpha]^{24}_D$ +229.0 (*c* 3.49, MeOH) [lit.[17] $[\alpha]^{25}_D$ +165 (*c* 0.15, MeOH), lit.[20] $[\alpha]^{27}_D$ +391.9 (*c* 1.47, MeOH)]; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.47 (s, 1H), 7.41 (t, *J* = 1.5 Hz, 1H), 6.43 (br s, 1H), 5.94 (s, 1H), 5.13 (s, 1H), 4.33 (q, *J* = 12.8 Hz, 2H), 2.25−2.39 (m, 2H), 1.41−1.51 (m, 3H), 1.02 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 165.8, 157.3, 143.0, 141.2, 136.7, 132.5, 120.1, 110.2, 110.0, 80.7, 62.8, 37.1, 29.7, 22.0, 16.0.

*(+)-(E)-Methyl 5-Hydroxy-4,4-dimethyl-7-oxonon-2-enoate (**17**).* To a solution of anhydrous (+)-α-pinene (ee = 86.5%) (0.639 mL, 4 mmol) in anhydrous diethyl ether (1.15 mL) at −10 °C was added chloroborane methyl sulfide complex (0.199 mL, 1.9 mmol) dropwise. The solution was slowly warmed to room temperature and stirred overnight. The resultant (+)-DIP-Cl solution (1 M, 1.8 equiv) was then cooled to −78 °C and DIPEA (461 μL, 2.65 mmol, 2.5 equiv) added, followed by slow dropwise addition of anhydrous 2-butanone (134 μL, 1.5 mmol, 1.4 equiv) in anhydrous diethyl ether (2 mL). The clear solution slowly changed to a cloudy white mixture which was stirred for 30 min at −78 °C and then slowly warmed to 0 °C and stirred for an additional 1.5 h. The resultant boron enolate solution was then cooled to −105 °C using an EtOH/$N_{2(l)}$ bath, and the aldehyde **16** (167 mg, 1.07 mmol) in anhydrous diethyl ether (2 mL) was added dropwise over 30 min. The resultant solution was kept at this temperature for 30 min, then warmed to −78 °C and stirred for 4 h. The mixture was then kept in a dry ice/acetone bath inside a freezer to slowly warm to −30 °C overnight. A 1:1:1 mixture of MeOH/30% H_2O_2/pH 7 phosphate buffer (15 mL) was then added and the resultant mixture stirred at 0 °C for 1 h. It was then extracted with diethyl ether (3 × 40 mL), and the combined organic extracts were washed with $Na_2S_2O_7$ (1 M, 30 mL, CAUTION: ADD SLOWLY) to destroy any remaining peroxides. The mixture was separated and the organic phase washed with brine, followed by drying over $MgSO_4$ and filtering to give a crude oil. Purification by column chromatography (petroleum ether/ethyl acetate, 4:1) yielded the titled compound as a colorless oil (115.7 mg, 47%): enantiomeric excess 92.5%; $[\alpha]^{24}_D$ +42.6 (*c* = 1.16, $CHCl_3$); ^{1}H NMR (500 MHz $CDCl_3$) δ = 6.95 (d, *J* = 16.1 Hz, 1H), 5.77 (d, *J* = 16.1 Hz, 1H), 3.84 (dt, *J* = 10.4, 2.2 Hz, 1H), 3.68 (s, 3H), 3.17 (d, *J* = 3.2 Hz, 1H), 2.48 − 2.34 (m, 4H), 1.04 (s, 3H), 1.03 (s, 3H), 0.99 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 212.2, 167.1, 154.7, 119.3, 73.4, 51.5, 43.9, 40.8, 36.8, 23.0, 22.1, 7.4; LRMS (ESI) *m*/*z* $[M + Na]^+$ for $C_{12}H_{20}O_4Na$ calcd 251.13, found 251.09; HRMS (ESI) *m*/*z* $[M + Na]^+$ for $C_{12}H_{20}O_4Na$ calcd 251.1254, found 251.1247.

*(+)-Methyl 2-(2,2,6-Trimethyl-5-oxocyclohex-3-enyl)acetate (**18**).* Under argon, a suspension of potassium hydride (30% w/w in mineral oil, ∼1.8 g, 4 equiv) was rinsed of oil using anhydrous toluene (3 × 5 mL) and then anhydrous toluene (180 mL) added and the mixture cooled to 0 °C. To the resultant suspension under argon was added a solution of (+)-**17** (ee = 92.5%) (800 mg, 3.5 mmol) in anhydrous toluene (30 mL) dropwise with stirring. The suspension was stirred at 0 °C for 30 min and then allowed to warm to room temperature and stirred for further 1 h. The reaction was cautiously quenched by the dropwise addition of a solution of acetic acid (0.77 mL) in toluene (20 mL) to attain a neutral pH, followed by water (100 mL). The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 50 mL). The organic extracts were combined, washed with saturated $NaHCO_3$, dried over Na_2SO_4, filtered, and concentrated in vacuo to give a crude yellow oil. Column chromatography (petroleum ether/ethyl acetate, 4:1) provided **18** as a clear oil (512 mg, 69%) as a mixture of diastereomers (22:78, syn/anti): enantiomeric excess 90%; ^{1}H NMR (500 MHz $CDCl_3$) δ = 6.57 (d, *J* = 12.6 Hz, 1H), 5.85 (d, *J* = 12.6 Hz, 1H), 3.67 (s, 3H), 2.60−2.10 (m, 4H), 1.13 (s, 3H), 1.08 (d, *J* = 7.7 Hz, 3H), 1.01 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 200.8, 173.7, 158.9, 125.9, 51.9, 46.3, 43.3, 42.0, 36.6, 28.0, 20.3, 11.8; LRMS (ESI) *m*/*z* $[M + Na]^+$ for $C_{12}H_{18}O_3Na$ calcd 233.12, found 233.10; HRMS (ESI) *m*/*z* $[M + Na]^+$ for $C_{12}H_{18}O_3Na$ calcd 233.1148, found 233.1144.

*N-(4-Bromophenyl)-2-((1S,6S)-2,2,6-trimethyl-5-oxocyclohex-3-en-1-yl)acetamide (**19**).* To the ester (**18**) (30 mg, 0.14 mmol) in MeOH (0.9 mL) was added a solution of LiOH·H_2O (60 mg, 1.43 mmol) in H_2O (0.3 mL). The resultant solution was stirred at room temperature for 2 h and then acidified to pH 2 with 1 M HCl. The mixture was extracted with EtOAc (4 × 4 mL), and the combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. Column chromatography (19:1 diethyl ether:MeOH) of the residue yielded a clear colorless oil (27.6 mg, 100%).

To the above carboxylic acid (27.6 mg, 0.14 mmol) in DMF (1 mL) was added 4-bromoaniline (24.2 mg, 0.14 mmol) at 0 °C. Following addition of DIPEA (26.5 μL, 0.15 mmol) and COMU (66 mg), the reaction mixture was stirred for 1 h at 0 °C and then 1 h at room temperature. TLC displayed an identical Rf of starting material to product, so the mixture was stirred overnight, before dilution with ethyl acetate (15 mL). The organic mixture was then washed with 1 M HCl (2 × 3 mL), saturated $NaHCO_3$solution (2 × 3 mL), and brine (2 × 3 mL). The organic mixture was then dried over Na_2SO_4 and concentrated in vacuo. Following column chromatography, the *anti* diastereoisomer (1*S*,6*S*) was isolated as an oil which solidified upon standing. It was then recrystallize from diethyl ether to give a mixture of colorless crystals and amorphous solids (26.3 mg). The *syn* diastereoisomer (1*S*,6*R*) was also isolated as a colorless oil (14.8 mg): combined yield 83.4%; mp 138−139 °C; ^{1}H NMR (400 MHz $CDCl_3$) δ = 7.40 (m, 4H), 7.19 (br s, 1H), 6.60 (d, *J* = 10 Hz, 1H), 5.88 (d, *J* = 10 Hz, 1H), 2.58 (dd, *J* = 16; 2.8 Hz, 1H), 2.50 (m, 1H), 2.33 (sextet, *J* = 6.7 Hz, 1H), 2.22 (dd, *J* = 7.5, 15.9 Hz, 1H), 1.17 (s, 3H), 1.14 (d, *J* = 6.8 Hz, 3H), 1.05 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ =200.7, 170.0, 159.0, 136.8, 132.0, 126.0, 121.3, 44.9, 43.5, 38.1, 36.5, 29.7, 28.1, 20.7, 12.2; LRMS (ESI) *m*/*z* $[M + Na]^+$ for $C_{17}H_{20}BrNO_2Na$ calcd 372.1, 374.1, found 372.1, 374.1; HRMS (ESI) *m*/*z* $[M + Na]^+$ for $C_{17}H_{20}BrNO_2Na$ calcd 372.0570, 374.0550, found 372.0572, 374.0552.

*(S)-Methyl 2-(3-Methoxy-2,6,6-trimethylcyclohexa-2,4-dien-1-yl)-acetate (**10**).* To a solution of the cyclohex-2-enone (**18**) (512 mg, 2.43 mmol) in freshly distilled CH_2Cl_2 (25 mL), in a sealed tube under argon was added 2,6-di-*tert*-butyl-4-methylpyridine (2.00 g, 9.73 mmol), and methyl trifluoromethanesulfonate (1.13 mL, 9.95 mmol). The resultant mixture was stirred at 90 °C for 4 h. The reaction vessel was allowed to cool to room temperature, diluted with

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ethyl acetate (300 mL), and washed with water (150 mL), saturated $NaHCO_3$ solution (150 mL) and brine (150 mL). The organic phase was dried with Na_2SO_4, filtered, and concentrated in vacuo to give a colorless oil. The oil was purified by column chromatography (1:10 → 1:4 ethyl acetate:petroleum spirit) to give the titled compound (387 mg, 71%) as a clear oil: $[\alpha]^{23}_D$ −203.5 (*c* 3.87, $CHCl_3$); ^{1}H NMR (300 MHz $CDCl_3$) δ = 5.78 (d, *J* = 9.9 Hz, 1H), 5.37 (d, *J* = 9.9 Hz, 1H), 3.63 (s, 3H), 3.49 (s, 3H), 2.47 (dd, *J* = 7.5, 14.8 Hz, 1H), 2.26 (t, *J* = 6.5 Hz, 1H), 2.13 (dd, *J* = 5.7, 15.0 Hz, 1 H), 1.66 (s, 3H), 1.04 (s, 3H), 0.96 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 174.4, 146.6, 137.2, 119.9, 116.6, 57.4, 51.6, 47.2, 35.0, 32.9, 26.4, 24.5, 14.7; GC/MS *m*/*z* 224.2 ($M^{+\bullet}$, 13.0), 152.2 (13.5), 151.1 (100), 149.1 (34.5), 136.2 (35.8), 135.2 (11.6), 121.1 (12.5), 119.2 (12.7), 105.2 (11.9), 91.1 (32.7), 79.1 (14.3), 77.1 (19.7), 43.1 (11.1), 41.1 (22.5); HRMS (EI) *m*/*z* $[M]^+$ for $C_{13}H_{20}O_3$ calcd 224.1412, found 224.1415.

*(+)-Cipadonoid B (**4**) and Diastereoisomers **13** and **15**.* A solution of (−)-**10** (ee = 83%) (387 mg, 1.73 mmol), (+)-**6** (ee > 99%, obtained from chiral chromatography[20]) (202.8 mg, 0.78 mmol), and *p*-toluenesulfonic acid (27 mg, 0.16 mmol, 20%) in anhydrous xylenes (5 mL) was stirred for 4 h at 180 °C in a sealed tube under argon. Following cooling to room temperature, the reaction mixture was diluted with CH_2Cl_2 (75 mL), washed with saturated $NaHCO_3$ solution and brine, dried over Na_2SO_3, and concentrated to give a yellow oil. Purification using column chromatography on silica (1:4 ethyl acetate:petroleum spirit), gave **4** (88.5 mg, 25%), **11** (69.8 mg, 20%), **13** (25.8 mg, 7%), and **15** (30.0 mg, 9%). Reheating **11** in xylenes at 180 °C in a sealed tube under argon gave additional crops of **4** to give an overall yield of 34%.

(+)-Cipadonoid B (**4**) white amorphous solid: $[\alpha]^{22}_D$ +296.4 (*c* 1.07, $CDCl_3$) [lit.[16] $[\alpha]^{20}_D$ +294.4 (*c* 0.015, $CHCl_3$)]; ^{1}H NMR (500 MHz $CDCl_3$) δ = 7.43 (m, 1H), 7.37 (m, 1H), 6.67 (d, *J* = 10.0 Hz, 1H), 6.39 (d, *J* = 1.5 Hz, 1H), 6.00 (s, 1H), 5.91 (d, *J* = 10.5 Hz, 1H), 5.48 (d, *J* = 1.5 Hz, 1H), 5.29 (s, 1H), 5.01 (s, 1H), 3.69 (s, 3H), 2.83 (dd, *J* = 6.0, 4.5 Hz, 1H), 2.43 (m, 3H), 2.04 (dq, *J* = 15.5, 3.0 Hz, 1H), 1.74 (m, 1H), 1.38 (td, *J* = 14.0, 4.5 Hz, 1H), 1.11 (s, 9H), 1.06, (dt, *J* = 13.5, 4.5 Hz, 1H), 0.97 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 203.5, 174.1, 166.2, 166.0, 159.1, 143.4, 142.7, 141.1, 127.0, 121.4, 120.4, 111.6, 110.1, 79.9, 52.1, 50.7, 47.6, 43.6, 39.3, 37.1, 31.7, 30.2, 29.5, 24.0, 21.1, 21.0, 18.5; LRMS (ESI) *m*/*z* $[M + Na]^+$ for $C_{27}H_{32}O_6Na$ calcd 475.21, found 475.20; HRMS (ESI) *m*/*z* $[M + Na]^+$ for $C_{27}H_{32}O_6Na$ calcd 475.2091, found 475.2089.

Compound **15**: slightly yellow oil: ;^{1}H NMR (500 MHz $CDCl_3$) δ = 7.50 (m, 1H), 7.41 (m, 1H), 6.47 (d, *J* = 10.5 Hz, 1H), 6.44 (d, *J* = 1.5 Hz, 1H), 5.94 (s, 1H), 5.83 (d, *J* = 10.0 Hz, 1H), 5.25 (s, 1H), 5.18 (s, 1H), 4.71 (s, 1H), 3.70 (s, 3H), 3.14 (t, *J* = 5.5 Hz, 1H), 2.68 (dd, *J* = 16.5, 4.5 Hz, 1H), 2.54 (m, 2H), 1.88 (m, 1H), 1.81 (m, 1H), 1.73 (m, 1H), 1.29 (ddd, *J* = 13.5, 6.5, 3.5 Hz, 1H), 1.20 (s, 3H), 1.07 (s, 3H), 1.05 (s, 3H), 0.96 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 202.2, 173.8, 166.5, 164.9, 155.4, 143.2, 143.1, 141.2, 124.5, 120.7, 120.1, 113.1, 110.0, 79.9, 54.7, 52.2, 48.5, 43.5, 39.5, 37.4, 32.7, 31.4, 31.0, 23.0, 22.0, 18.7, 17.6; LRMS (ESI) *m*/*z* $[M + Na]^+$ for $C_{27}H_{32}O_6Na$ calcd 475.21, found 475.20; HRMS (ESI) *m*/*z* $[M + Na]^+$ for $C_{27}H_{32}O_6Na$ calcd 475.2091, found 475.2094.

Compound **13**: colorless crystals (MeOH); mp 195 − 196 °C; ^{1}H NMR (500 MHz $CDCl_3$) δ = 7.51 (m, 1H), 7.39 (t, *J* = 1.5 Hz, 1H), 6.59 (d, *J* = 10.0 Hz, 1H), 6.46 (m, 1H), 5.82 (d, *J* = 10.0 Hz, 1H), 5.74 (s, 1H), 5.49 (s, 1H), 5.42 (d, *J* = 1.5 Hz, 1H), 5.39 (s, 1H), 3.69 (s, 3H), 2.92 (dd, *J* = 8.1, 3.0 Hz, 1H), 2.63 (dd, *J* = 6.3, 3.3 Hz, 1H), 2.45 (dd, *J* = 8.5, 17.0 Hz, 1H), 2.37 (dd, *J* = 17.0, 2.5 Hz, 1H), 2.19 (td, *J* = 13.0, 4.0 Hz, 1H), 1.99 (dq, *J* = 4.2, 14.7 Hz, 1H), 1.69 (m, 1H), 1.19 (s, 3H), 1.13 (dt, *J* = 4.2, 13.5 Hz, 1H), 1.07 (s, 3H), 1.02 (s, 3H), 0.96 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 203.1, 174.5, 166.2, 165.6, 158.8, 143.4, 142.7, 141.2, 127.8, 122.0, 120.4, 112.3, 110.2, 79.9, 52.1, 47.0, 44.1, 39.6, 37.0, 31.7, 29.4, 29.3, 24.4, 22.1, 19.4, 18.4; LRMS (ESI) *m*/*z* $[M + Na]^+$ for $C_{27}H_{32}O_6Na$ calcd 475.21, found 475.20; HRMS (ESI) *m*/*z* $[M + H]^+$ for $C_{27}H_{33}O_6$ calcd 453.2272, found 453.2272.

*(S,S)-2,3-Epoxycipadonoid B (**20**).* To a stirring solution of (−)-cipadonoid B (**4**) (19.8 mg, 0.044 mmol) in MeOH (3.8 mL) at 0 °C was added 30% H_2O_2 (77 μL, 0.679 mmol) dropwise. The solution was stirred for 15 min, followed by the addition of saturated aqueous solution of K_2CO_3 (240 μL). The mixture was then allowed to warm to room temperature and stirred overnight before pouring into 0.1 M HCl (20 mL). The mixture was then extracted with CH_2Cl_2 (3 × 25 mL), and the combined organic extracts were dried over Na_2SO_3. Following filtration, the solvent was removed in vacuo to give an oil that was purified by column chromatography (1:1 → 2:1 diethyl ether/petroleum ether) affording the titled compound **20** (15.8 mg, 75%) as a single diastereoisomer, which was recrystallized from chloroform producing colorless needles: mp 207−209 °C; $[\alpha]^{23}_D$ +178.2 (*c* 1.58, $CDCl_3$); ^{1}H NMR (500 MHz $CDCl_3$) δ = 7.45 (m, 1H), 7.38 (t, *J* = 1.7 Hz, 1H), 6.40 (m, 1H), 5.42 (d, *J* = 1.6 Hz, 1H), 5.16 (s, 1H), 5.09 (s, 1H), 3.68 (s, 3H), 3.45 (d, *J* = 4.6 Hz, 1H), 3.28 (d, *J* = 4.5 Hz, 1H), 3.02 (dd, *J* = 3; 8.5 Hz, 1H), 2.57 (d, 4.6 Hz, 1H), 2.26 (m, 3H), 1.73 (m, 1H), 1.48 (m, 1H), 1.26 (m, 2H), 1.10 (s, 3H), 1.01 (s, 3H), 0.96 (s, 3H), 0.91 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ = 210.4, 173.8, 165.4, 165.4, 142.9, 142.3, 141.0, 122.2, 120.1, 112.5, 109.9, 80.4, 66.0, 57.7, 52.0, 51.7, 48.9, 40.7, 39.4, 36.3, 31.4, 30.1, 26.8, 21.7, 20.2, 19.9, 18.3; LRMS (ESI) *m*/*z* $[M + Na]^+$ for $C_{27}H_{32}O_7Na$ calcd 491.2, found 491.3; HRMS (ESI) *m*/*z* $[M + Na]^+$ for $C_{27}H_{32}O_7Na$ calcd 491.2040, found 491.2043.

*(−)-Proceranolide (**2**).* To a solution of **20** (10 mg, 0.021 mmol) in EtOH/H_2O/THF/saturated $NaHCO_3$ (87:48:30:3 v/v, 1 mL) under argon was added freshly amalgamated aluminum pieces (prepared from aluminum foil[57]). The reaction mixture was sonicated (Unisonics FXP12 M ultrasonic cleaner, 150 W, 40 kHz) at room temperature and monitored by TLC with additional aluminum pieces added if required. After 1 h, ethyl acetate (1 mL) was added, the mixture filtered through a plug of diatomaceous earth, and the filter cake washed with additional ethyl acetate (1 mL). The organic extract was dried with $MgSO_4$, filtered, and concentrated in vacuo to give a colorless oil (12 mg). HPLC [Phenomenex luna C18(2) (250 mm × 4.6 mm × 5 μm) methanol water gradient] of the crude mixture gave proceranolide (**2**) (3 mg, 30%): $[\alpha]^{22}_D$ −116.5 (*c* 0.125, $CHCl_3$) [lit.[12] $[\alpha]^{20}_D$ −141 (*c* 0.70, $CHCl_3$)]; ^{1}H NMR (500 MHz $CDCl_3$) δ = 7.54 (m, 1H), 7.37 (t, *J* = 1.7 Hz, 1H), 6.47 (m, 1H), 5.56 (s, 1H), 4.04 (dt, *J* = 21; 2.5 Hz, 1H), 3.72 (d, *J* = 10 Hz, 1H), 3.67 (s, 3H), 3.44 (dt, *J* = 21; 2.5 Hz, 1H), 3.22 (dd, *J* = 10.5; 2.8 Hz 1H), 3.17 (dd, *J* = 14; 2.5 Hz, 1H), 3.02 (m, 1H), 2.34 (m, 1H), 1.95 (m, 2H), 1.76 (m, 3H), 1.10 (s, 3H), 1.01 (s, 3H), 0.79 (s, 3H), 0.71 (s, 3H); ^{13}C NMR (500 MHz, $CDCl_3$) δ =219.9, 174.4, 171.5, 142.6, 141.7, 131.3, 128.2, 120.8, 110.1, 80.2, 53.6, 52.0, 51.8, 50.0, 39.3, 39.3, 37.9, 33.5, 33.3, 33.1, 28.6, 25.3, 23.8, 20.1, 18.7, 17.5, 16.9; LRMS (ESI) *m*/*z* $[M + Na]^+$ for $C_{27}H_{34}O_7Na$ calcd 493.2, found 493.3; HRMS (ESI) *m*/*z* $[M + Na]^+$ for $C_{27}H_{34}O_7Na$ calcd 493.2197, found 493.2204.

*(−)-Khayasin (**1**).* To a stirring solution of proceranolide (**2**) (13.2 mg, 0.028 mmol) in CH_2Cl_2 (400 μL) were successively added *N*,*N*-dimethylaminopyridine (13.7 mg, 0.112 mmol, 4 equiv), isobutyric acid (5.26 μL, 0.058 mmol, 2 equiv), and EDCI (16.1 mg, 0.084 mmol, 3 equiv). The resultant solution was stirred at room temperature for 4 h and gradually darkened to orange and then brown. When the reaction was deemed complete (TLC), the mixture was diluted with diethyl ether (1 mL) and 0.2 M HCl (1 mL) added. The organic phase was separated and the remaining aqueous phase extracted with diethyl ether (2 × 1 mL). The combined organic extracts were then washed with saturated $NaHCO_3$ and brine, dried over $MgSO_4$, and passed through a plug of silica. Concentration in vacuo gave a clear oil. Following column chromatography (CH_2Cl_2/ethyl acetate, 9:1), khayasin (**1**) was obtained as a white solid (10.7 mg, 71%): $[\alpha]^{24}_D$ −87.2 (*c* 1.02, acetone) [lit.[3] $[\alpha]^{25}_D$ −79.5 (*c* 0.86, acetone)]; ^{1}H NMR (500 MHz $CDCl_3$) δ = 7.53 (m, 1H), 7.39 (t, *J* = 1.7 Hz, 1H), 6.45 (m, 1H), 5.65 (s, 1H), 5.28 (s, 1H), 4.94 (d, *J* = 10 Hz, 1H), 3.71 (d, *J* = 20 Hz, 1H), 3.68 (s, 3H), 3.43 (dt, *J* = 20 Hz; 3 Hz, 1H), 3.22 (dd, *J* = 9 Hz, 3.6 Hz, 1H), 3.14 (m, 1H), 2.78 (dd, *J* = 15; 2 Hz, 1H), 2.63 (septet, *J* = 7 Hz, 1H) 2.35 (m, 2H), 2.10 (m, 1H), 2.03 (br s, 1H), 1.79 (m, 1H), 1.72 (m, 2H), 1.21 (d, *J* = 7 Hz, 3H), 1.19 (d, *J* = 7 Hz, 3H), 1.13 (s, 3H), 1.09 (m, 1H), 1.04 (s, 3H), 0.79 (s, 3H), 0.70 (s, 3H); ^{13}C NMR (500 MHz, $CDCl_3$) δ = 218.1, 176.6, 174.2, 170.0, 142.8, 141.7, 131.7, 127.8, 120.6, 109.9, 80.7, 78.0, 52.9, 52.2, 52.1, 48.1, 40.8, 38.5, 38.1, 34.4, 33.5, 33.2, 29.1, 23.2, 20.6, 19.9, 18.8, 18.6,

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17.8, 16.7; LRMS (ESI) m/z $[M + Na]^+$ for $C_{31}H_{40}O_8Na$ calcd 563.3, found 563.3; HRMS (ESI) m/z $[M + Na]^+$ for $C_{31}H_{40}O_8Na$ calcd 563.2621, found 563.2624.

(−)-Mexicanolide (3). To a cold (0 °C) stirring solution of proceranolide (**2**) (5.9 mg, 0.013 mmol) in acetone (500 μL) was added dropwise Jones reagent (chromic acid solution from $K_2Cr_2O_7$ and H_2SO_4 in acetone) until an orange color persisted. The mixture was stirred for an additional 15 min before being diluted with diethyl ether (1 mL). The mixture was filtered through a plug of silica and $MgSO_4$ and concentrated in vacuo to give an oil. Column chromatography (CH_2Cl_2/MeOH 49:1) gave the titled compound mexicanolide (**3**) as a colorless oil (4 mg, 68%), identical in all respects to the natural product: $[\alpha]^{23}_D$ −37.2 (*c* 0.08, $CHCl_3$) [lit.[12] $[\alpha]^{25}_D$ −90 ($CHCl_3$)]; ^{1}H NMR (500 MHz $CDCl_3$) δ = 7.56 (m, 1H), 7.38 (t, J = 1.7 Hz, 1H), 6.47 (m, 1H), 5.24 (s, 1H), 3.70 (s, 3H), 3.47 (m, 2H), 3.20 (m, 2H), 2.74 (dd, J = 8.3; 4.7 Hz, 1H), 2.47 (m, 2H), 2.29 (m, 1H), 2.08 (m, 1H), 1.80 (m, 3H), 1.23 (s, 3H), 1.11 (m, 1H), 0.99 (s, 3H), 0.97 (s, 3H), 0.86 (s, 3H); ^{13}C NMR (500 MHz, $CDCl_3$) δ = 213.1, 211.1, 173.7, 169.9, 142.9, 141.7, 134.0, 125.5, 120.5, 110.1, 80.8, 58.1, 54.4, 52.4, 50.6, 49.5, 40.3, 38.1, 36.6, 33.1, 32.4, 28.9, 22.1, 18.7, 18.1, 18.0, 17.5; LRMS (ESI) m/z $[M + Na]^+$ for $C_{27}H_{32}O_7Na$ calcd 491.2, found 491.2; HRMS (ESI) m/z $[M + Na]^+$ for $C_{27}H_{32}O_7Na$ calcd 491.2040, found 491.2052.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H and ^{13}C NMR spectra of new compounds, natural products and selected intermediates. X-ray crystal data. Computational methods and calculated enthalpies. 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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