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Total Synthesis | *Very Important Paper*

# VIP Total Synthesis of (−)-Dolastatrienol

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**Abstract:** The first asymmetric total synthesis of the tricyclic diterpenoid natural product (−)-dolastatrienol has been accomplished using a rhodium(II)-catalyzed carbene cyclization cycloaddition cascade reaction as the key step to construct the [5.4.0]carbobicyclic core. An intramolecular Heck reaction furnished the tricyclic skeleton and a challenging methylenation completed the synthesis of the target.

## Introduction

The dolastanes are a family of more than 30 marine diterpenes bearing linearly fused 5,7,6-tricyclic carbon frameworks (Figure 1).[1,2] Dolatriol (**1**) was the first dolastane discovered,

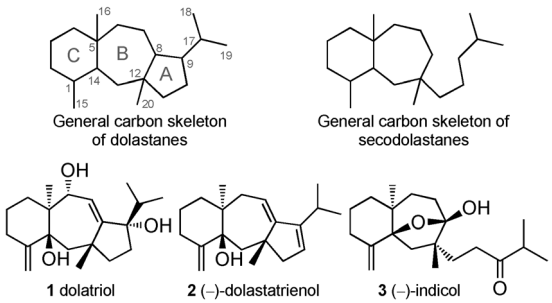


**Figure 1.** Dolastanes and secodolastanes.

and was isolated from the sea hare *Dolabella auricularia* from the Indian Ocean in 1976. It was reported to be cytotoxic against the P-388 lymphocytic leukemia cell line.[3] Dolastatrienol (**2**) was isolated from a mixture of two brown algae *Dictyota linearis* and *Dictyota Divaricata* in 1982.[4] These sources suggested that the dolastanes originated from the algae and were accumulated in algal-feeding *Dolabella* through its diet.[2c] In fact, it is known that some species of *Dictyota* produce metabolites of dolastanes, such as seco-secodolastanes **3**, as defense chemicals to deter feeding by herbivores.[5]

The members of the dolastanes family are characterized by a *trans* relative stereochemistry between the angular methyl groups at C5 and at C12. They are diversified within the basic carbon skeleton in the degree and positions of oxygenation and unsaturation. The majority of the dolastanes have exocyclic methylene groups at C1 and are oxygenated at C14, and hence are allylic alcohols, as are both **1** and **2**.

The syntheses of *rac*-**2**[6] and *ent*-**2**[7] have been reported. In these syntheses, each ring of the molecule was assembled in a linear manner, attaining a perhyroazulene AB ring system as the first bicyclic intermediate, and the C ring was added last. Our group has also engaged in the studies of natural products related to the dolastanes. In 2007, we accomplished the total synthesis of (−)-indicol.[8] Our synthesis featured the construction of the [5.4.0]carbobicyclic core using a rhodium-catalyzed carbene cyclization cycloaddition cascade in one step. This success encouraged us to extend our studies toward the synthesis of the tricyclic dolastanes. Herein, we report our efforts that culminated in the total synthesis of dolastatrienol (**2**), the first asymmetric synthesis of the natural enantiomer of this dolastane natural product.

## Results and Discussion

### Retrosynthetic Analysis.

Our retrosynthetic strategy of **2** is shown in Scheme 1. We envisioned that **2** could be obtained from tricyclic ketone **R1** by methylenation. The tricyclic diene skeleton can be constructed from vinyl triflate **R2** through an intramolecular Heck reaction. Reductive elimination of chloride **R3** would reveal the latent hydroxy group at C14 and concomitantly functionalize C7 and C8 in **R2** in preparation for the Heck reaction. Intermediate **R3** could be derived from functionalization of ketone **4**, which is an intermediate in our total synthesis of (−)-indicol. The tricyclic skeleton of ketone **4** has been constructed using a rhodium-catalyzed carbene cyclization cycloaddition cascade reaction (CCCC) in one step from α-diazoketone **5**. This diazoketone was derived from commercially available protected glycidol (*S*)-**6**.

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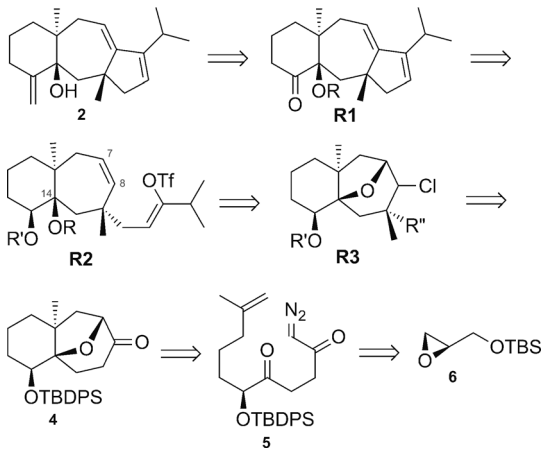
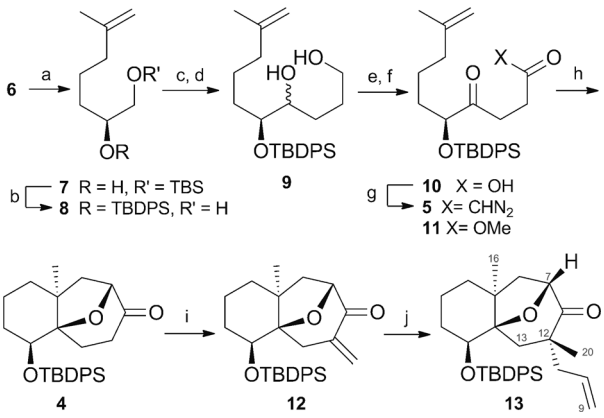



**Scheme 1.** Retrosynthetic analysis.




**Scheme 2.** Synthesis of bicyclic ketone **13**. Reagents and conditions: (a) $CH_3(C{=}CH_2)CH_2CH_2MgBr$, CuCN, THF, −78 °C, 5 h, 99%; (b) TBDPSCl, imidazole, DMF, rt, O/N; 12 M HCl, *i*PrOH, 0 °C, 2 h, 98%; (c) $(COCl)_2$, DMSO, DCM; $Et_3N$, −78 °C, 2 h; (d) $ClMg(CH_2)_3OMgCl$, THF, −78 °C, 1.5 h, 77% over 2 steps; (e) $(COCl)_2$, DMSO, DCM; $Et_3N$, −78 °C, 2 h; (f) $NaClO_2$, $NaH_2PO_4$, 2-methyl-2-butene, *t*BuOH, $H_2O$, rt, O/N, 76% over 2 steps; (g) (i) NaH, THF, 0 °C, 30 min, 0.02 M in THF; (ii) *i*BuOCOCl (3.5 equiv), 2 h; (iii) $CH_2N_2$ (6.6 equiv), 0 °C to rt, 36 h, **5** (59%), **11** (22%); (h) 1 mol% $Rh_2(Oct)_4$, 4 Å molecular sieves, DCM, 0 °C, O/N, 56%; (i) $CH_2Br_2$, $Et_2NH$, MeCN, 80 °C, 100 W microwave, 30 min, 85%; (j) $Me_2Cu(CN)Li_2$, $CH_2{=}CHSnBu_3$, THF, 78 °C, 1 h; MeI, 30 °C to rt, 1 h, 94%.

### Synthesis of Ketone 4

Our first task involving the synthesis of **2** was to secure multigram quantities of bicyclic ketone **4**, by a route largely similar to the one used in the synthesis of (−)-indicol with a CCCC reaction. We have had a long standing interest in the application of this reaction to construct oxapolycycles and natural products.[9] In this one-step, metal-catalyzed reaction, three σ bonds are formed, and up to four new stereocenters are generated. The oxabicyclic scaffold assembled by the CCCC reaction shows a strong steric bias, and the facial selectivity of transformations that occur on the molecule are highly predictable. By subsequently cleaving the oxygen bridge in the oxabicyclic framework, stereochemically-defined hydroxylated carbocyclic derivatives are also accessible.[10] Other research groups have applied this reaction to the synthesis of complex natural products, including aspidophytine,[11] gallicadiol and isogallicadiol,[12] polygalolides A and B,[13] and platensimicin.[14] We have applied this reaction to the total syntheses of (−)-pseudolaric acid A,[15a] (−)-indicol,[8] and synthetic studies towards isocurcumenol.[15b]

The synthesis of **2** began with the ring opening of oxirane (*S*)-**6** by the cuprate derived from 3-methylbut-3-enylmagnesium bromide, and this afforded alcohol **7** with the first stereogenic centre (Scheme 2). To increase the efficiency of the route, the silylation of secondary alcohol **7** with *tert*-butyldiphenylsilyl chloride (TBDPSCl) was worked up using 12 M HCl in *i*PrOH, to accomplish in one pot a concomitant deprotection of the *tert*-butyldimethylsilyl group, to afford alcohol **8** without silyl group migration. This protocol eliminated one step from the previous synthetic route. Swern oxidation of primary alcohol **8** provided an aldehyde that was treated with Normant's Grignard reagent to give diol **9**.[16] Bis-oxidation of diol **9** under the Swern conditions, followed by Lindgren oxidation,[17] led to γ-ketoacid **10**.

The typical preparation of the diazoketone involved treatment of the acid with chloroformate in the presence of triethylamine to form the mixed anhydride, then reaction with diazomethane. This reaction was capricious, and was accompanied by the formation of varying but substantial amounts of methyl ester **11**, and we surmised that the ammonium salt formed during the activation interfered with the diazomethane acylation. To increase the yield of **5**, NaH was used as a base to deprotonate acid **10**, and then isobutyl chloroformate (3.5 equiv) in dilute solution (0.04 M) was added to the carboxylate to ensure a complete conversion to the mixed anhydride, followed by the addition of a large excess of ethereal diazomethane. In this manner, consistent yields (52–59%) of the desired **5** were obtained, even on a scale involving 40 g of **10**. However, the formation of **11** (15–22%) could not be entirely avoided.

The key CCCC reaction of **5** was executed on a large scale initiated by a catalytic amount of $Rh_2(Oct)_4$, and this afforded the desired diastereomer **4** as the major product in an isolated yield of 56%, along with other minor diastereomers (Scheme 2).[8] Thus a total of 13.0 g (29.0 mmol) of the cycloadduct **4** was obtained from 245 mmol of (*S*)-TBS-protected glycidol **6** through a linear sequence of eight steps with an overall yield of 12%, which corresponds to an average yield of 77% per step.

### Synthesis of Bicyclic Ketone 13

A α-bisalkylation of ketone **4** through its enolate should directly provide **13**. However, based on our previous studies on the synthesis of indicol, the direct alkylation of **4** was very difficult to achieve owing to the sterically demanding OTBDPS group.[8] We had considered changing the protecting group, but this would add unproductive, functional group interconversion steps to the synthesis. Alternatively, ketone **4** was converted into α-methylene ketone **12** by treatment with dibromomethane and diethylamine under microwave irradiation (Scheme 2). As the reaction site in **12** was further removed

from the steric congestion, functionalizations were accomplished readily. Exploiting the stereochemical bias of **12**, addition of vinylcuprate, followed by trapping of the resultant enolate with MeI, established the correct stereochemistry at the quaternary carbon C12 of ketone **13** in excellent yield and diastereoselectivity in one pot. The nOe correlations between H20↔H7 and H20↔H13β, but not H20↔H13α, showed that the methyl group was on the β-face of **13**. Furthermore, a correlation between H9↔H16 indicated that the allyl group was on the α-face.

### Cleavage of the Oxygen Bridge

Our attempts so far to form the final ring, and then induce the cleavage of the ether, were unsuccessful. The tricyclic framework presumably prevented the orbital alignment that is required for C–O bond cleavage. It became clear that the oxygen bridge must be cleaved prior to the final cyclization.

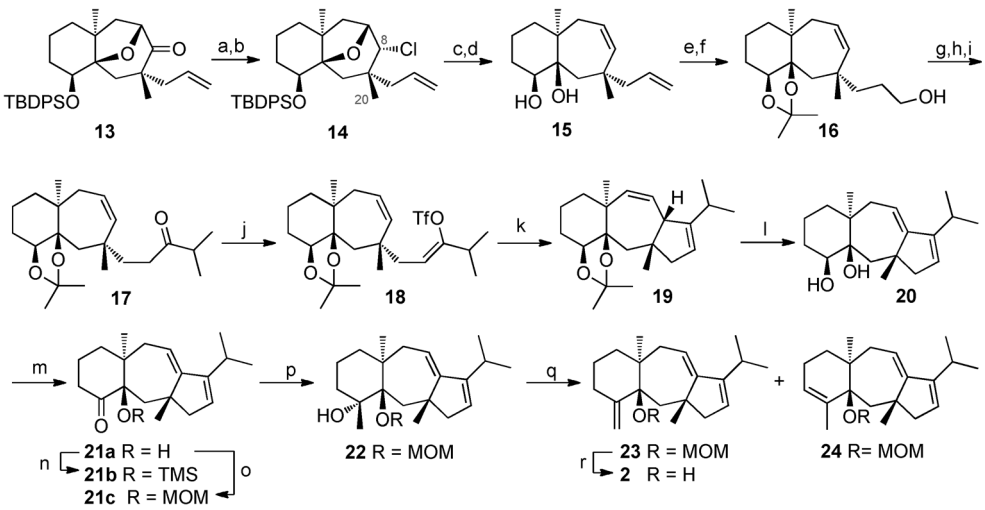
In the event, ketone **13** was reduced smoothly to give an alcohol that was converted into chloride **14** (Scheme 3). The alcohol was deprotonated with sodium hydride, before treatment with thionyl chloride to attempt to increase the reaction rate. However, the reaction was still very sluggish. After refluxing for three days, chloride **14** with a diastereomeric ratio of 10:1 was obtained in 75% yield based on a recovery of 26% of **13**. The major diastereomer was the α-chloride as shown in Scheme 3, as indicated by nOe correlations between H8↔H20.

On a 10 mg scale, chloride **14** underwent oxygen bridge cleavage as well as desilylation when refluxed with sodium metal in 1,2-dimethoxyethane (DME), and afforded the diol **15** directly. But after scaling up, the same protocol afforded **15** in a diminished yield. This decrease in yield appeared to be related to some hydroxide generated in situ under the reaction conditions, which were sufficient to desilylate all the silyl groups in small scale reactions, but became less effective on larger scale, such that a mixture of silylated and desilylated alcohols were obtained. To avoid obtaining this mixture, the crude product obtained from the reductive elimination was treated with *tetra-n*-butylammonium fluoride (TBAF), enabling diol **15** to be obtained cleanly as the sole product. The yield over two steps was reproducible and consistently over 80%.

### The Heck Reaction and the Synthesis of Diene 21

The *syn* vicinal diol **15** was protected as an acetonide under standard conditions.[18] The less sterically encumbered olefin underwent regioselective hydroboration with disiamylborane to give primary alcohol **16** in high yield after oxidation.[19] From alcohol **16**, the remaining isopropyl moiety was installed smoothly through a three-step sequence of Dess–Martin periodinane (DMP) oxidation, addition of *i*PrMgCl, and a second DMP oxidation to give ketone **17.** Treatment of this ketone with freshly prepared potassium 1,1,1,3,3,3-hexamethyldisilazide (KHMDS)>, generated the kinetic enolate which was trapped by *N*-phenyltriflimide, to give vinyl triflate **18** as the only observed regio- and geometric isomer.

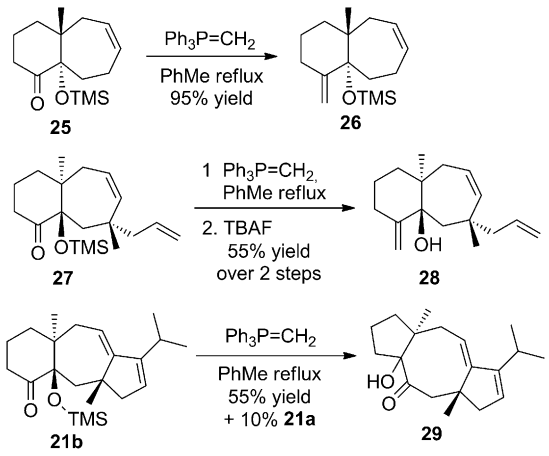
Subsequently, **18** was induced to undergo a Heck cyclization by refluxing in acetonitrile in the presence of $[Pd(PPh_3)_4]$, with $K_2CO_3$ as the base.[20] The side chain approached the cycloheptene preferentially from the α-face to give a *cis*-fused cyclization product. The skipped diene **19**, resulting from a *syn* Pd–H elimination, was obtained. When **19** was heated with DOWEX resin in methanol, isomerization to the desired conjugated diene occurred, with concomitant cleavage of the acetonide to give diol **20**. Vicinal *syn* diol **20** was oxidized into the corresponding α-hydroxy ketone **21a**. Whereas DMP and Swern oxidations failed, this transformation was successful using *o*-iodoxybenzoic acid (IBX).




**Scheme 3.** Synthesis of tricyclic dolastatrienol **2**. Reagents and conditions: (a) $NaBH_4$, DCM, MeOH 0 °C to rt, O/N, 100%. (b) NaH, THF, 1 h; $SOCl_2$, reflux, 3 d, 54% isolated yield, 26% starting material recovered, 75% yield brsm; (c) Na, DME, reflux, O/N; (d) TBAF/THF, rt, 2.5 h, 85% over 2 steps; (e) 2-methoxypropene, PTSA, DCM, 0 °C, 30 min, 79%; (f) $(Sia)_2BH$, THF, 0 °C,1 h; $NaOH_{(aq)}$, $H_2O_{2(aq)}$, 0 °C to rt, 30 min, 83%; (g) DMP, DCM, rt, 30 min; (h) *i*PrMgCl, THF, 0 °C, 30 min; (i) DMP, DCM, rt, 30 min, 64% over 3 steps; (j) KHMDS, THF, −78 °C, 1 h; $PhNTf_2$, 1 h, −78 °C; (k) $[Pd(PPh_3)_4]$, $K_2CO_3$, 4 Å molecular sieves, MeCN, reflux, 30 min, 87% over 2 steps; (l) DOWEX 50WX8-100, MeOH, reflux, 2 days, 88%; (m) IBX, EtOAc, reflux, 4 h, 88%; (n) TMSOTf, 2,6-lutidine, DCM, 0 °C, 1 h, 57%; (o) MOMCl, NaI, DIPEA, DME, reflux, O/N 80%. (p) MeLi, THF, 1 h, 41% isolated yield, **21c** recovered (49%), 79% yield brsm, (q) Burgess reagent, PhMe, 15 min, **23** (31%), **24** (20%); (r) HCl, *i*PrOH, 65 °C, 6 h, 71%.

### Methylenation to Synthesize 2

Having arrived at ketone **21a**, the final challenge was to transform the carbonyl group into the exocyclic methylene group in **2**. This olefination turned out to be much more difficult than expected. As the amount of **21a** was limited, we first examined the reaction using model substrates **25** and **27** (Scheme 4). Both of these bicyclic models underwent successful olefination




**Scheme 4.** Wittig methylenation of substrates.

with methylene triphenylphosphorane. However, after **21 a** was silylated as **21 b**, under the same reaction conditions, an α-ketol rearrangement occurred instead of methylenation to generate [5,8,5]-tricyclic **29**. Methylenation using the Peterson, Tebbe, Petasis, Nysted, or Lombardo reagents also failed to induce any reaction.[21] The successful Wittig reactions with model substrates **25** and **27**, but not with the tricyclic **21 b**, clearly showed that the failure was due to the presence of the additional, distal five membered ring. While this ring appeared to be quite far from the reaction site at C1, increased steric crowdedness at C1 could be induced by compression of the substituents imposed by the additional ring (Figure 2).

We surmised that the Wittig and other methylenation reagents are too bulky to attack the sterically encumbered carbonyl group. After further investigations, a methylation-dehydration strategy was the most viable solution. Thus, alcohol

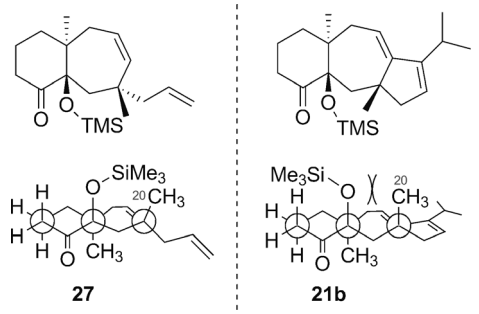



**Figure 2.** Conformations of **27** and **21 b**.

**21 a** was protected as methoxymethyl (MOM) ether **21 c** (Scheme 3). Nucleophilic addition of methyllithium to **21 c** suffered from a low conversion, probably due to competing enolization of the hindered ketone, so the yield of alcohol **22** was enriched by repeating several rounds of addition. An nOe signal between the C15 methyl protons and the methylene protons of MOM showed that these groups are *cis*, implying that methyllithium attacked the carbonyl group on the face opposite the angular methyl group. Then **22** was dehydrated using the Burgess reagent to afford the desired exocyclic methylene **23** as the major product (30% yield), along with the endocyclic olefin **24** (20%). Finally, acid-promoted MOM deprotection furnished the target molecule dolastatrienol **2**. The spectroscopic data of synthetic **2** thus obtained, corresponded to the characterization of the natural product in the literature.[4] The optical rotation of our synthetic **2** is $[\alpha]_D^{20} = -191$ ($c = 0.04$, $CHCl_3$), compared with $[\alpha]_D^{20} = +200$ ($c = 0.25$, $CHCl_3$) of its enantiomer previously synthesized.[7c]

## Conclusions

We have accomplished the total synthesis of (−)-dolastatrienol **2** using an intramolecular carbene cyclization-cycloaddition cascade reaction to construct rings BC, an oxygen bridge ring cleavage, then an intramolecular Heck reaction to furnish ring A. The final methylenation turned out to be challenging because of the rigidity conferred by ring A, which led to conformational changes, resulting in an unexpected and accentuated steric congestion at the reaction site. The required olefination was finally accomplished by a methylation–dehydration strategy. This approach could be applied to the synthesis of dolastatrienol analogues, for generating libraries of compounds with this scaffold for bioactivity screening.

## Experimental Section

All reactions were performed in over-dried flasks under argon. Solvents and solution reagents were transferred with syringes or cannulae using standard inert atmosphere techniques. Chemicals were purified according to literature procedures, and solvents were freshly distilled before use. $Et_2O$ and tetrahydrofuran (THF) were distilled over potassium/sodium/benzophenone ketyl, or granular $CaH_2$. MeCN, $CH_2Cl_2$ (DCM), diisopropylethylamine (DIPEA), DMSO (under reduced pressure), DME, HMDS, 2,6-lutidine, PhMe, and $Et_3N$ were distilled over granular $CaH_2$. *iso*-Butylchloroformate, $(COCl)_2$, and trimethylsilyl trifluoromethanesulfonate (TMSOTf) were purified by distillation. Diazomethane was prepared from Diazald using Aldrich diazomethane kits with clear glass joints. Microwave synthesis was carried out using a CEM Discover LabMate. Reactions were monitored by TLC using E. Merck 0.2 mm pre-coated silica gel plates (Kieselgel 60 $F_{254}$). Components were visualized by illumination with a short-wavelength UV light and/or staining in anisaldehyde, vanillin, or phosphomolybdic acid followed by heating. Flash column chromatography was performed on E. Merck silica gel 60 (230–400 mesh ASTM). All $^1H$ and $^{13}C$ NMR spectra were recorded on a Bruker DPX 300, 400 or 500 MHz Fourier Transform Spectrometer operating at 300 MHz, 400 MHz or 500 MHz for $^1H$ and at 75 MHz, 100 MHz or 125 MHz, respectively, for $^{13}C$. All spectra were calibrated at $\delta = 7.26$ ppm for $^1H$ in $CHCl_3$ and $\delta = 77.03$ ppm for $^{13}C$ in $CDCl_3$ or at $\delta = 7.16$ ppm for $^1H$ in $C_6H_6$ and $\delta = 128.0$ ppm for $^{13}C$ in $C_6D_6$. Spectral features were designated as follows: s = singlet, d = doublet, t = triplet, q = quartet, sept = septet, m = mutiplet, and br = broad. IR absorption spectra were recorded for samples in DCM solution on a Bio-Rad Fourier Transform 165 Spectrophotometer from 4000 $cm^{-1}$ to 400 $cm^{-1}$. Mass spectra were obtained on a Finnigan MAT 95 mass spectrometer for both low resolution and high resolution, with accurate mass reported for the molecular ion ($M^+$) or the next largest fragment ions. Melting points were measured on Zeiss Asiolab Microscope using a Linkam

TC92 temperature controller. Optical rotations were recorded on a PerkinElmer 343 polarimeter.

Detailed and additional experimental procedures for the preparation and characterization of compounds **4**, **5**, **7**–**11**, **25**, **26**, **28**, and **29**, and the spectra of all new compounds are available in the Supporting Information.

Synthesis of **12:** To a solution of **4** (0.2163 g, 0.4821 mmol) in MeCN (4 mL) in a vial was added $CH_2Br_2$ (1.0 mL, 7.124 mmol) and $Et_2NH$ (1.40 mL, 13.5 mmol). The vial was sealed with a septum and irradiated at 100 W at 80 °C for 30 min in the microwave reactor. The reaction was cooled to room temperature, concentrated, diluted with $Et_2O$, and washed with saturated $NH_4Cl$ (aq). The combined organic layers were dried (anhyd. $MgSO_4$) and concentrated in vacuo. The residue was purified by flash chromatography using 5% EtOAc in hexane to afford **12** (0.1896 g, 85% yield) as a yellow oil. **12**: $R_f$ (20% EtOAc in hexane) 0.63; IR ($CH_2Cl_2$): $\tilde{\nu}$ = 3073, 3047, 2961, 2935, 2860, 1716 (ketone C=O), 1617, 1472, 1464, 1428 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ = 7.70–7.72 (m, 4H), 7.36–7.45 (m, 6H), 6.12 (s, 1H), 5.23 (s, 1H), 4.47 (dd, $J$ = 9.1, 3.4 Hz, 1H), 3.60 (dd, $J$ = 11.6, 5.1 Hz, 1H), 3.53 (dt, $J$ = 17.1, 2.7 Hz, 1H), 2.32 (d, $J$ = 17.1, 1H), 2.11 (dd, $J$ = 13.4, 9.1 Hz, 1H), 1.75 (dddd, $J$ = 12.5, 12.2, 11.6, 4.1 Hz, 1H), 1.55–1.59 (m, 2H), 1.48–1.54 (m, 1H), 1.38–1.44 (m, 1H), 1.23–1.25 (m, 1H), 1.06–1.16 (m, 1H), 1.04 (s, 9H), 0.97 ppm (s, 3H); $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$ = 196.9, 139.5, 136.0 (2C), 135.9 (2C), 134.2, 133.6, 129.7, 129.6, 127.7 (2C), 127.4 (2C), 123.0, 86.2, 78.1, 73.3, 45.3, 44.1, 38.8, 32.9, 30.7, 27.1 (3C), 21.2, 20.9, 19.5 ppm; LRMS (EI): $m/z$ (%): 403 ($M^+-C_4H_9$, 24), 385 (8), 325 (6), 227 (8), 200 (17), 199 (100), 149 (16); HRMS (EI): calcd for $C_{25}H_{27}O_3Si$ ($M^+-C_4H_9$) 403.1729, found 403.1743; $[\alpha]_D^{20}$ = −15.1 ($c$ = 0.63, $CHCl_3$).

Synthesis of **13**: To pre-dried CuCN (0.330 g, 3.687 mmol) suspended in THF (2 mL) in a Schlenk flask was added MeLi (0.77 M, 8.3 mL, 0.6369 mmol) and tributylvinyltin (0.98 mL, 3.352 mmol) at 0 °C. The resultant pale grey solution was stirred at room temperature for 1.5 h. Compound **12** (0.7585 g, 1.646 mmol) in THF (4 mL) was added through a cannula at −78 °C. The reaction was allowed to warm to room temperature. After 1 h, MeI (3 mL) was added at 0 °C. The reaction was quenched with saturated $NH_4Cl$ (aq) and extracted with $Et_2O$. The combined organic layers were dried (anhyd. $MgSO_4$) and concentrated in vacuo. The residue was purified by flash chromatography using 5% EtOAc in hexane to afford **13** (0.7796 g, 94% yield) as a colorless oil. $R_f$ (20% EtOAc in hexane) 0.67; IR ($CH_2Cl_2$): $\tilde{\nu}$ = 3074, 3047, 2963, 2935, 2861, 1719 (ketone C=O), 1638, 1471, 1428 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ = 7.77–7.78 (m, 4H), 7.38–7.47 (m, 6H), 5.62–5.70 (m, 1H), 5.11 (dd, $J$ = 18.2, 10.4 Hz, 2H), 4.41 (dd, $J$ = 9.5, 4.2 Hz, 1H), 3.64 (dd, $J$ = 11.7, 4.4 Hz, 1H), 2.55 (dd, $J$ = 13.5, 5.8 Hz, 1H), 2.29 (d, $J$ = 14.3 Hz, 1H), 1.94–1.98 (m, 2H), 1.73 (m, 1H), 1.71 (d, $J$ = 14.4 Hz, 1H), 1.45 (s, 3H), 1.38–1.47 (m, 2H), 1.24–1.33 (m, 2H), 1.09–1.13 (m, 1H), 1.04 (s, 9H), 0.95 (s, 3H), 0.91–1.00 ppm (m, 1H); $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$ = 214.1, 136.0 (2C), 135.7 (2C), 134.84, 134.81, 133.4, 129.8, 129.4, 127.7 (2C), 127.3 (2C), 118.6, 85.6, 77.7, 74.0, 45.8, 44.6, 43.0, 41.7, 37.9, 30.5, 30.1, 29.9, 27.1 (3C), 21.1, 19.6, 19.4 ppm; LRMS (EI): $m/z$ 445 ($M^+-C_4H_9$, 16), 385 (4), 279 (7), 199 (9), 167 (24), 153 (24), 149 (100); HRMS (EI): calcd for $C_{28}H_{33}O_3Si$ ($M^+-C_4H_9$) 445.2199, found 455.2198; $[\alpha]_D^{20}$ = −15.6 ($c$ = 0.82, $CHCl_3$).

Synthesis of **14:** A solution of **13** (1.072 g, 2.132 mmol) in MeOH (20 mL) and DCM (20 mL) at 0 °C was treated with $NaBH_4$ (1.04 g, 27.5 mmol) in several portions. The mixture was stirred overnight at room temperature. The reaction was quenched with saturated $NH_4Cl$ (aq) and extracted with $Et_2O$. The combined organic layers were dried (anhyd. $MgSO_4$) and concentrated in vacuo to afford the crude alcohol as a white solid. Part of the above crude alcohol (0.5858 g, 1.161 mmol) in THF (25 mL) was treated with NaH (60% w/w, 0.096 g, 2.32 mmol) at 0 °C for 1 h. After the addition of thionyl chloride (0.6 mL, 8.12 mmol), the reaction was heated under reflux for 3 days. The reaction was quenched with pH 7 phosphate buffer and extracted with $Et_2O$. The combined organic layers were dried (anhyd. $MgSO_4$) and concentrated in vacuo. The residue was purified by flash chromatography using 5%–20% EtOAc in hexane to afford **14** (0.3393 g, 54% isolated yield, 26% starting material recovered, 75% yield brsm) as a yellow oil. **14**: $R_f$ (10% EtOAc in hexane) 0.72; IR ($CH_2Cl_2$): $\tilde{\nu}$ = 2969, 2933, 2896, 2855, 1719, 1638, 1592, 1471, 1428, 1389 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.74 (ddd, $J$ = 17.4, 7.6, 1.5 Hz, 4H), 7.36–7.45 (m, 6H), 5.82–5.92 (m, 1H), 5.10 (dd, $J$ = 17.7, 1.9 Hz, 1H), 5.06 (dd, $J$ = 10.9, 1.9 Hz, 1H), 4.41 (ddd, $J$ = 12.6, 5.7, 4.2 Hz, 1H), 3.83 (d, $J$ = 3.8 Hz, 1H), 3.71 (dd, $J$ = 11.7, 4.3 Hz, 1H), 2.61 (dd, $J$ = 13.9, 7.2 Hz, 1H), 2.46 (dd, $J$ = 13.9, 7.2 Hz, 1H), 2.12 (d, $J$ = 12.5 Hz, 1H), 1.87–2.00 (m, 2H), 1.66 (d, $J$ = 12.7 Hz, 1H), 1.63–1.74 (m, 2H), 1.30–1.38 (m, 2H), 1.27 (s, 3H), 1.03–1.18 (m, 1H), 1.02 (s, 9H), 0.84–0.93 (m, 1H), 0.72 ppm (s, 3H); $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$ = 136.5, 136.0 (2C), 135.8 (2C), 134.9, 133.6, 129.7, 129.4, 127.6 (2C), 127.3 (2C), 116.7, 88.6, 85.6, 71.1, 55.6, 45.9, 43.3, 41.9, 40.8, 38.3, 32.2, 30.8, 29.0, 27.1 (3C), 22.4, 20.0, 19.5 ppm; LRMS (EI): $m/z$ 545 ([$M$+Na]$^+$, 79), 527 (100), 515 (4), 487 (6), 437 (4), 409 (7), 231 (7); HRMS (EI): calcd for $C_{32}H_{43}O_2NaSiCl$ ([$M$+Na]$^+$), 545.2618, found 545.2647; $[\alpha]_D^{20}$ = −9.04 ($c$ = 2.08, $CHCl_3$).

Synthesis of **15:** Finely cut pieces of sodium (0.968 g, 42.1 mmol) were added to a solution of **14** (0.5124 g, 0.9793 mmol) in 25.0 mL DME. The reaction was heated under reflux overnight to yield a deep purple solution. The supernatant liquid was collected in a new flask via cannula, to which water was added. The aqueous layer was acidified with 1 M HCl and the mixture was extracted with $Et_2O$. The combined organic layers were dried (anhyd. $MgSO_4$) and concentrated in vacuo to yield a brown residue. The residue was treated with TBAF (1.0 M, 2.5 mL) for 2.5 h. The reaction was quenched with saturated $NH_4Cl$ (aq) and extracted with $Et_2O$. The combined organic layers were dried (anhyd. $MgSO_4$) and concentrated in vacuo. The residue was purified by flash chromatography using 15% EtOAc in hexane to afford **15** (0.2085 g, 85% yield) as a colorless oil. **15**: $R_f$ (20% EtOAc in hexane) 0.45; IR ($CH_2Cl_2$): $\tilde{\nu}$ = 3614 (O–H), 3091, 3010, 2936, 2872, 2855, 1651, 1634, 1460 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ = 5.81–5.89 (m, 1H), 5.49 (dd, $J$ = 11.9, 1.8 Hz, 1H), 5.44 (ddd, $J$ = 11.9, 8.4, 2.9 Hz, 1H), 5.01–5.07 (m, 2H), 3.56 (dd, $J$ = 10.6, 5.0 Hz, 1H), 2.72 (d, $J$ = 15.9 Hz, 1H), 2.09 (dd, $J$ = 13.6, 6.3 Hz, 1H), 1.98 (dd, $J$ = 13.6, 8.2 Hz, 1H), 1.82 (d, $J$ = 15.2 Hz, 1H), 1.64–1.73 (m, 2H), 1.64 (d, $J$ = 15.2 Hz, 1H), 1.25–1.59 (m, 4H), 1.21 (s, 3H), 0.97–1.18 (m, 1H), 0.95 ppm (s, 3H); $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$ = 138.7, 135.5, 125.9, 117.5, 79.0, 72.6, 51.7, 40.1, 39.5, 29.4, 38.4, 36.6, 30.4, 28.5, 20.5, 19.8 ppm; LRMS (EI): $m/z$ 273 ([$M$+Na]$^+$, 100), 271 (5), 261 (15); HRMS (EI): calcd for $C_{16}H_{26}O_2Na$ ([$M$+Na]$^+$) 273.1830, found 273.1813; $[\alpha]_D^{20}$ = −55.9 ($c$ = 1.08, $CHCl_3$).

Synthesis of **16:** A solution of **15** (0.3759 g, 1.501 mmol) in DCM (45 mL) was treated with 2-methoxypropene (0.43 mL, 4.490 mmol) and *p*-toluenesulfonic acid (PTSA; 0.001 g, 0.005 mmol) at 0 °C. After stirring for 30 min, it was poured into saturated $NaHCO_3$ (aq). The aqueous layer was extracted with $Et_2O$. The combined organic layers were dried (anhyd. $MgSO_4$) and concentrated in vacuo. The residue was purified by flash chromatography using 2% EtOAc in hexane to afford the acetal (0.3422 g, 79% yield) as a colorless oil. The acetal (0.0628 g, 0.216 mmol) in THF (2 mL) was treated with $(Sia)_2BH$ (prepared from $BH_3$-DMS (DMS = dimethyl sulfide; 10 M, 0.065 mL, 0.65 mmol), 2-methyl-2-butene (0.155 mL, 1.46 mmol) in 5.0 mL THF) at 0 °C for 1 h. NaOH (1 M, 1.5 mL) and $H_2O_2$ (10%,

1.5 mL) were added at 0 °C. After 30 min at room temperature, the layers were separated and the aqueous layer was extracted with $Et_2O$. The combined organic layers were dried (anhyd. $MgSO_4$) and concentrated in vacuo. The residue was purified by flash chromatography using 30% EtOAc in hexane to afford **16** (0.0553 g, 83% yield) as a colorless oil. **16**: $R_f$ (20% EtOAc in hexane) 0.28; IR ($CH_2Cl_2$): $\tilde{\nu}$ = 3627 (O-H), 3046, 2991, 2951, 2878, 1606, 1458 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ = 5.34 (ddd, $J$ = 12.7, 7.6, 2.2 Hz, 1H), 5.18 (dd, $J$ = 12.8, 1.7 Hz, 1H), 3.96 (dd, $J$ = 2.8, 2.3 Hz, 1H), 3.64, (t, $J$ = 6.5 Hz, 2H), 2.53 (d, $J$ = 16.9 Hz, 1H), 2.08 (d, $J$ = 14.6 Hz, 1H), 1.90–1.97 (m, 1H), 1.61–1.80 (m, 6H), 1.50–1.60 (m, 4H), 1.47 (s, 3H), 1.38 (s, 3H), 1.23 (s, 3H), 1.00 (s, 3H), 0.90 ppm (dd, $J$ = 13.0, 7.9 Hz, 1H); $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ = 137.2, 124.6, 106.5, 84.9, 83.0, 63.7, 45.2, 42.8, 40.3, 39.8, 39.2, 32.3, 31.2, 28.2, 27.3, 26.3, 21.8, 21.5, 14.3 ppm; LRMS (EI): $m/z$ 331 ($[M+Na]^+$, 39), 301 (51), 289 (100), 251 (8), 212 (11), 149 (10); HRMS (EI): calcd for $C_{19}H_{32}O_3Na$ ($[M+Na]^+$) 331.2249, found 331.2202; $[\alpha]_D^{20}$ = +13.6 ($c$ = 0.86, $CHCl_3$).

Synthesis of **17:** A solution of **16** (0.0457 g, 0.148 mmol) in DCM (25 mL) was treated with DMP (0.3 M in DCM, 1 mL, 0.3 mmol) for 30 min at room temperature. The reaction was quenched with saturated $Na_2S_2O_3$ and saturated $NaHCO_3$, then extracted with DCM. The combined organic layers were dried (anhyd. $MgSO_4$) and concentrated in vacuo to afford a crude aldehyde as a colorless oil. The aldehyde was taken up in THF (1 mL) and treated with freshly prepared *i*PrMgCl (1 M in THF, 0.50 mL, 0.50 mmol) at 0 °C. The reaction was stirred at room temperature for 30 min, then quenched with saturated $NH_4Cl$ (aq). The layers were separated and the aqueous layer was extracted with $Et_2O$. The combined organic layers were dried (anhyd. $MgSO_4$) and concentrated in vacuo to afford an alcohol as a colorless oil. The crude alcohol was taken up in 25 mL DCM and treated with DMP (0.3 M in DCM, 1 mL, 0.3 mmol) for 30 min at room temperature. The reaction was quenched with saturated $Na_2S_2O_3$ and saturated $NaHCO_3$, then extracted with DCM. The combined organic layers were dried (anhyd. $MgSO_4$) and concentrated in vacuo. The residue was purified by flash chromatography using 5% EtOAc in hexane to afford **17** (0.0330 g, 64% yield over 3 steps) as a colorless oil. **17**: $R_f$ (10% EtOAc in hexane) 0.44; IR ($CH_2Cl_2$): $\tilde{\nu}$ = 2969, 2954, 2931, 2878, 1708 (ketone C=O), 1459, 1411, 1380 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 5.36 (ddd, $J$ = 12.7, 7.6, 2.2 Hz, 1H), 5.13 (dd, $J$ = 12.8, 1.8 Hz, 1H), 3.96 (dd, $J$ = 2.8, 2.3 Hz, 1H), 2.63 (septet, $J$ = 6.9 Hz, 1H), 2.47–2.55 (m, 3H), 1.99 (d, $J$ = 14.6 Hz, 1H), 1.91–1.95 (m, 1H), 1.61–1.79 (m, 3H), 1.48–1.64 (m, 5H), 1.47 (s, 3H), 1.38 (s, 3H), 1.24 (s, 3H), 1.09 (d, $J$ = 6.9 Hz, 6H), 1.00 (s, 3H), 0.88–0.93 ppm (m, 1H); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 215.1, 136.5, 125.5, 106.5, 84.7, 82.9, 45.1, 41.0, 40.3, 40.0, 39.7, 39.2, 36.3, 32.2, 31.2, 27.2, 26.2, 21.8, 21.4, 18.41, 18.40, 14.3 ppm; LRMS (EI): $m/z$ 348 ($M^+$,14), 291 (11), 273 (23), 208 (50), 190 (100); HRMS (EI): calcd for $C_{22}H_{36}O_3$ ($M^+$) 348.2664, found 348.2653; $[\alpha]_D^{20}$ = +44.9 ($c$ = 0.99, $CHCl_3$).

Synthesis of **18:** A solution of **17** (0.0245 g, 0.0703 mmol) in THF (15 mL) was treated with freshly prepared KHMDS (2.0 mL, 0.24 M in THF) at −78 °C for 1 h, then with $PhNTf_2$ (0.0789 g, 0.210 mmol) as a solution in THF (2 mL). The reaction was allowed to warm to room temperature. After 1 h, the reaction was quenched with saturated $NH_4Cl$ (aq) and extracted with $Et_2O$. The combined organic layers were dried (anhyd. $MgSO_4$) and concentrated in vacuo. The residue was purified by flash chromatography using 3% EtOAc in hexane to afford **18** as a colorless oil, which was used directly in the next step. $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ = 5.37–5.44 (m, 2H), 5.19 (dd, $J$ = 12.8, 1.4 Hz, 1H), 3.97 (dd, $J$ = 2.7, 2.3 Hz, 1H), 2.55–2.60 (m, 1H), 2.54 (d, $J$ = 17.4 Hz, 1H), 2.24 (dd, $J$ = 14.6, 9.6 Hz, 1H), 2.04 (ddd, $J$ = 14.7, 5.2, 1.8 Hz, 1H), 2.00 (d, $J$ = 14.9 Hz, 1H), 1.91–1.96 (m, 1H), 1.66–1.80 (m, 3H), 1.54–1.64 (m, 1H), 1.50 (dd, $J$ = 17.3, 7.8 Hz, 1H), 1.47 (s, 3H), 1.39 (s, 3H), 1.38 (d, $J$ = 14.9 Hz, 1H), 1.28 (s, 3H), 1.13 (d, $J$ = 6.7 Hz, 3H), 1.12 (d, $J$ = 6.7 Hz, 3H), 0.97 (s, 3H), 0.91 ppm (dd, $J$ = 13.1, 8.3 Hz, 1H); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 156.0, 135.9, 126.0, 118.0 (q, $J$ = 319.4 Hz, $CF_3$), 116.1, 106.5, 84.6, 82.9, 45.1, 42.2, 40.7, 40.3, 39.3, 32.5, 32.3, 31.2, 27.2, 26.2, 21.9, 21.4, 20.31, 20.25, 14.2 ppm; LRMS (EI): $m/z$ 480 ($M^+$, 2), 465 (2), 407 (2), 405 (2), 340 (3), 323 (1), 289 (3), 249 (12), 192 (13), 191 (87); HRMS (EI): calcd for $C_{23}H_{35}O_5F_3{}^{32}S$ ($M^+$) 480.2152, found 480.2159; $[\alpha]_D^{20}$ = +4.58 ($c$ = 0.48, $CHCl_3$).

Synthesis of **19**: Compound **18** obtained from the last step was taken up in MeCN (15 mL), to which was added 4 Å molecular sieves and $K_2CO_3$ (0.0148 g, 0.107 mmol). The reaction mixture was degassed, then treated with $[Pd(PPh_3)_4]$ (0.0971 g, 0.084 mmol). The reaction mixture was heated to reflux. After 10 min, the reaction mixture was cooled, and poured into saturated $NH_4Cl$ (aq). The reaction mixture was extracted with $Et_2O$, and the combined organic layers were dried (anhyd. $MgSO_4$) and concentrated in vacuo. The residue was purified by flash chromatography using 1.5% EtOAc in hexane to afford **19** (0.0202 g, 87% yield over 2 steps) as a colorless oil. **19**: $R_f$ (5% EtOAc in hexane) 0.63; IR ($CH_2Cl_2$): $\tilde{\nu}$ = 3054, 2990, 2959, 2931, 2872, 2836, 1460 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ = 5.59 (dd, $J$ = 11.9, 8.9 Hz, 1H), 5.48 (d, $J$ = 11.9 Hz, 1H), 5.29 (br, s, 1H), 3.90 (s, 1H), 3.17 (d, $J$ = 8.8 Hz, 1H), 2.35 (d, $J$ = 14.7 Hz, 1H), 2.26–2.28 (m, 1H), 1.99–2.09 (m, 3H), 1.83–1.85 (m, 1H), 1.67–1.75 (m, 3H), 1.47 (d, $J$ = 14.7 Hz, 1H), 1.46 (s, 3H), 1.43 (s, 3H), 1.38 (s, 3H), 1.10–1.15 (m, 1H), 1.04 (d, $J$ = 6.8 Hz, 3H), 1.02 (s, 3H), 0.95 ppm (d, $J$ = 6.8 Hz, 3H); $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$ = 154.0, 143.0, 125.3, 118.8, 106.2, 84.1, 82.7, 55.6, 50.1, 47.5, 47.0, 41.9, 30.8, 30.5, 27.8, 27.5, 26.5, 22.6, 22.1, 22.0, 20.3, 14.2 ppm; LRMS (EI): $m/z$ 330 ($M^+$, 11), 272 (12), 229 (16), 201 (12), 191 (27); HRMS (EI): calcd for $C_{22}H_{34}O_2$ ($M^+$) 330.2553, found 330.2558; $[\alpha]_D^{20}$ = +52.8 ($c$ = 0.5, $CHCl_3$).

Synthesis of **20:** A solution of **19** (0.0130 g, 0.0393 mmol) in MeOH (15 mL) was treated with DOWEX 50WX8-100 (5 g) under reflux for two days. The reaction mixture was cooled, filtered through a short plug of $Na_2SO_4$ and a short plug of silica gel, and washed with $Et_2O$. The solvent was removed in vacuo and the residue was purified by flash chromatography using 20% EtOAc in hexane to afford **20** (0.0101 g, 88% yield) as white solid. **20**: $R_f$ (20% EtOAc in hexane) 0.34; IR ($CH_2Cl_2$): $\tilde{\nu}$ = 3603 (br, OH), 2932, 2875, 2362, 1458 $cm^{-1}$; $^1H$ NMR (500 MHz, $C_6D_6$): $\delta$ = 5.55 (s, 1H), 5.48 (dd, $J$ = 9.5, 4.4 Hz, 1H), 3.26 (dd, $J$ = 15.3, 4.0 Hz, 1H), 3.22 (dd, $J$ = 11.2, 4.8 Hz, 1H), 2.43–2.45 (m, 1H), 2.25 (d, $J$ = 16.6 Hz, 1H), 2.12 (dd, $J$ = 16.7, 2.8 Hz, 1H), 2.09 (dd, $J$ = 14.9 Hz, 1H), 1.89–1.95 (m, 1H), 1.71 (s, 1H), 1.55 (d, $J$ = 14.9 Hz, 1H), 1.48–1.57(m, 2H), 1.46 (s, 3H), 1.26–1.45 (m, 4H), 1.14 (d, $J$ = 6.8 Hz, 3H), 1.11 (d, $J$ = 6.8 Hz, 3H), 0.88 (s, 3H), 0.81–0.85 ppm (m, 1H); $^{13}C$ NMR (125 MHz, $C_6D_6$): $\delta$ = 154.9, 150.6, 125.5, 115.1, 79.5, 72.5, 51.3, 46.2, 41.8, 40.7, 36.8, 36.6, 30.7, 28.7, 26.3, 22.69, 22.66, 20.6, 20.4 ppm; LRMS (EI): $m/z$ 290 ($M^+$, 29), 272 (50), 257 (14), 239 (35), 229 (19), 211 (24), 201 (52); HRMS (EI): calcd for $C_{19}H_{30}O_2$ ($M^+$) 290.2240, found 290.2241; m.p. = 104 °C; $[\alpha]_D^{20}$ = −28.3 ($c$ = 0.59, $CHCl_3$).

Synthesis of **21 a:** A solution of **20** (0.0061 g, 0.021 mmol) in EtOAc (4 mL) was treated with IBX (0.0240 g, 0.085 mmol) at reflux for 5 h. After cooling to room temperature, the crude mixture was filtered through a short pad of silica gel. The solvent was removed in vacuo and the residue was purified by flash chromatography using 10% EtOAc in hexane to afford **21 a** (0.0053 g, 88% yield) as white solid. **21 a**: $R_f$ (20% EtOAc in hexane) 0.41; IR ($CH_2Cl_2$): $\tilde{\nu}$ = 3591, 2926, 2853, 1713, 1462, 1427 $cm^{-1}$; $^1H$ NMR (500 MHz, $C_6D_6$): $\delta$ = 5.49 (s, 1H), 5.34 (dd, $J$ = 9.4, 4.5 Hz, 1H), 3.13 (dd, $J$ = 14.7, 4.1 Hz, 1H), 2.92 (dt, $J$ = 13.1, 7.7 Hz, 1H), 2.30–2.37 (m, 1H), 2.29 (d, $J$ =

16.7 Hz, 1H), 2.18 (d, $J$=15.6 Hz, 1H), 2.12–2.18 (m, 1H), 2.02–2.07 (m, 2H), 1.54 (d, $J$=15.8 Hz, 1H), 1.48–1.64 (m, 2H), 1.45 (dd, $J$=15.3 9.5 Hz, 1H), 1.21 (s, 3H), 1.09 (d, $J$=6.9 Hz, 3H), 1.08 (d, $J$=7.0 Hz, 3H), 0.87- 0.91 (m, 1H), 0.77–0.80 (m, 1H), 0.77 ppm (s, 3H); $^{13}$C NMR (125 MHz, $C_6D_6$): $\delta$=211.7, 154.8, 149.7, 125.7, 113.9, 83.5, 50.7, 47.9, 43.8, 39.4, 35.8, 35.4, 34.4, 27.2, 25.9, 22.3, 22.2 (2C), 18.9 ppm; LRMS (EI): $m/z$ 288 ($M^+$, 38), 270 (12), 255 (13), 248 (14), 245 (13), 231 (11), 227 (32); HRMS (EI): calcd for $C_{19}H_{28}O_2$ ($M^+$) 288.2084, found 288.2090; m.p.=110 °C; $[\alpha]_D^{20}=-154.8$ ($c$=0.31, $CHCl_3$).

Synthesis of **21 c**: NaI (0.0270 g, 1.801 mmol) in DME (1.5 mL) was treated with MOMCl (360 μL, 4.74 mmol) for 10 min at 0 °C to generate a yellow solution. A solution of **21 a** (0.0061 g, 0.0211 mmol) and DIPEA (0.90 mL, 5.17 mmol) in DME (1.5 mL) was added. After heating under reflux overnight, saturated $NaHCO_3$ (aq) was added and the reaction mixture was extracted with $Et_2O$. The combined organic layers were washed with saturated NaCl (aq), dried (anhyd. $MgSO_4$) and concentrated in vacuo. The residue was purified by flash chromatography using 5% EtOAc in hexane to afford **21 c** (0.0056 g, 80% yield) as a white solid. **21 c**: $R_f$ (10% EtOAc in hexane) 0.53; IR ($CH_2Cl_2$): $\tilde{\nu}$=3062, 2989, 2957, 2927, 2872, 1708, 1460, 1381 cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$): $\delta$=5.58 (br, s, 1H), 5.36 (dd, $J$=9.5, 4.6 Hz, 1H), 4.71 (d, $J$=6.1 Hz, 1H), 4.61 (d, $J$=6.1 Hz, 1H), 3.46 (s, 3H), 3.17 (dd, $J$=15.5, 4.1 Hz, 1H), 3.09 (ddd, $J$=13.5, 13.2, 8.4 Hz, 1H), 2.32–2.43 (m, 3H), 2.17 (d, $J$=13.5, 4.9 Hz, 1H), 2.11 (dd, $J$=16.7, 2.8 Hz, 1H), 1.87 (d, $J$=15.8 Hz, 1H), 1.82–1.88 (m, 2H), 1.76 (d, $J$=16.3 Hz, 1H), 1.61 (dd, $J$=15.4, 9.5 Hz, 1H), 1.20 (s, 3H), 1.08 (d, $J$=6.8 Hz, 3H), 1.04 (d, $J$=6.8 Hz, 3H), 1.03–1.05 (m, 1H), 0.82 ppm (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$=214.0, 154.2, 149.3, 125.3, 113.5, 92.8, 88.0, 56.4, 50.5, 44.8, 44.4, 37.2, 35.2, 34.2, 33.7, 26.2, 25.5, 22.2, 22.1, 22.0, 19.0 ppm; LRMS (EI): $m/z$ 332 ($M^+$,18), 305 (16), 304 (10), 303 (49), 288 (14), 287 (37), 285 (16); HRMS (EI): calcd for $C_{21}H_{32}O_3$ ($M^+$) 332.2346, found 332.2346; m.p.=48–52 °C; $[\alpha]_D^{20}=-115.9$ ($c$=0.62, $CHCl_3$).

Synthesis of **22:** A solution of **21 c** (0.0047 g, 0.0141 mmol) in THF (1.0 mL) was treated with MeLi (1.12 M, 100 μL, 0.112 mmol) at room temperature for 1 h. The reaction was monitored by TLC and a low conversion was observed. The mixture was poured into saturated $NH_4Cl$ (aq) and extracted with $Et_2O$. The combined organic layers were dried (anhyd $MgSO_4$) and concentrated in vacuo. The residue was taken up in THF and resubjected to treatment with MeLi. After repeating 6 times, the residue was purified by flash chromatography using 10–15% EtOAc in hexane to recover unreacted **21 c** (0.0023 g, 49%) and give **22** (0.0020 g, 41% yield, 79% yield brsm) as white needles. **22**: $R_f$ (10% EtOAc in hexane) 0.31; IR ($CH_2Cl_2$): $\tilde{\nu}$=3061 (br, OH), 3024, 2991, 2957, 2926, 2870, 2855, 1462, 1421 cm$^{-1}$; $^1$H NMR (500 MHz, $C_6D_6$): $\delta$=5.56 (dd, $J$=9.7, 4.6 Hz, 1H), 5.55 (s, 1H), 4.91 (dd, $J$=7.1 Hz, 1H), 4.47 (dd, $J$=7.1 Hz, 1H), 3.38 (dd, $J$=15.0, 4.3 Hz, 1H), 3.25 (s, 3H), 2.44–2.47 (m, 1H), 2.56 (d, $J$=17.1 Hz, 1H), 2.07 (d, $J$=15.8 Hz, 1H), 2.00–2.20 (m, 4H), 1.91 (d, $J$=15.7 Hz, 1H), 1.45–1.49 (m, 1H), 1.42 (dd, $J$=15.2, 9.6 Hz, 1H), 1.39 (s, 3H), 1.25 (s, 3H), 1.21 (s, 3H), 1.15–1.18 (m, 1H), 1.16 (d, $J$=6.8 Hz, 3H), 1.13 (d, $J$=6.8 Hz, 3H), 1.05–1.08 ppm (m, 1H); $^{13}$C NMR (125 MHz, $C_6D_6$): $\delta$=153.4, 150.1, 124.4, 116.2, 92.9, 86.3, 76.2, 55.6, 51.3, 45.1, 43.2, 38.3, 37.5, 36.7, 33.7, 27.9, 26.9, 26.0, 23.6, 22.5, 22.3, 19.0 ppm; LRMS (EI): $m/z$ 348 ($M^+$, 6), 316 (15), 303 (29), 286 (50), 271 (11); HRMS (EI): calcd for $C_{22}H_{36}O_3$ ($M^+$) 348.2659, found 348.2651; m.p.=114–116 °C; $[\alpha]_D^{20}=-114.5$ ($c$=0.22, $CHCl_3$).

Synthesis of **23**: A solution of **22** (0.0055 g, 0.0156 mmol) in PhMe (0.8 mL) was treated with Burgess reagent (0.0106 g, 0.0445 mmol) at 70 °C for 1 h. The reaction mixture was diluted with EtOAc, poured into saturated $NaHCO_3$, and extracted with EtOAc. The combined organic layers were dried (anhyd. $MgSO_4$) and concentrated in vacuo. The residue was purified by flash chromatography using 50% DCM in hexane to afford **23** (0.0016 g, 31% yield) as a colorless oil, and **24** (0.0011 g, 20% yield) as a colorless oil. **23**: $R_f$ (50% DCM in hexane) 0.59; IR ($CH_2Cl_2$): $\tilde{\nu}$=2997, 2957, 2928, 2855, 1462, 1379 cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$): $\delta$=5.55 (br, s, 1H), 5.41 (dd, $J$=9.4, 4.6 Hz, 1H), 5.04 (s, 1H), 4.77(s, 1H), 4.64 (dd, $J$=5.3 Hz, 1H), 4.62 (dd, $J$=5.3 Hz, 1H), 3.45 (s, 3H), 3.18 (dd, $J$=14.6, 4.2 Hz, 1H), 2.50–2.57 (m, 1H), 2.38–2.40 (m, 1H), 2.27 (d, $J$=16.0 Hz, 1H), 2.03–2.14 (m, 3H), 1.82 (d, $J$=15.0 Hz, 1H), 1.75 (d, $J$=15.1 Hz, 1H), 1.56–1.63 (m, 2H), 1.49 (dd, $J$=15.3, 9.5 Hz, 1H), 1.29 (s, 3H), 1.09 (d, $J$=6.8 Hz, 3H), 1.05 (d, $J$=6.8 Hz, 3H), 0.96–0.99 (m, 1H), 0.85 ppm (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$=153.6, 151.0, 149.7, 124.6, 114.8, 112.8, 91.6, 84.2, 56.3, 51.1, 45.3, 42.6, 38.3, 37.3, 34.9, 32.9, 26.4, 25.6, 23.3, 22.3, 22.2, 19.9 ppm; LRMS (EI): $m/z$ 330 ($M^+$, 5), 269 (26), 268 (100), 254 (13), 253 (65); HRMS (EI): calcd for $C_{22}H_{32}O_2$ ($M^+-H_2$) 328.2397, found 328.2400; $[\alpha]_D^{20}=-33.7$ ($c$=0.15, $CHCl_3$). **24**: $R_f$ (50% DCM in hexane) 0.38; IR ($CH_2Cl_2$): $\tilde{\nu}$=2963, 2929, 2862, 1691, 1458, 1425, 1276, 1249 cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$): $\delta$=5.74 (s, 1H), 5.60 (br, s, 1H), 5.55 (dd, $J$=8.5, 5.7 Hz, 1H), 4.81 (d, $J$=7.2 Hz, 1H), 4.59 (d, $J$=7.2 Hz, 1H), 2.60 (dd, $J$=14.2, 5.5 Hz, 1H), 2.44 (sept, $J$=6.8 Hz, 1H), 2.38 (d, $J$=16.1 Hz, 1H), 2.22 (dd, $J$=7.9, 7.4 Hz, 1H), 2.16 (dd, $J$=16.4, 2.7 Hz, 1H), 2.00–2.08 (m, 1H), 1.87 (dt, $J$=12.1, 5.7 Hz, 1H), 1.76 (dd, $J$=14.0, 8.9 Hz, 1H), 1.70–1.73 (m, 1H), 1.36 (s, 3H), 1.19 (s, 3H), 1.11 (d, $J$=6.8 Hz, 3H), 1.06 (d, $J$=6.8 Hz, 3H), 1.06 ppm (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$=153.3, 129.9, 124.8, 113.6, 91.4, 89.1, 55.2, 48.0, 42.0, 41.5, 39.3, 38.1, 37.1, 31.3, 28.7, 27.9, 25.7, 22.0, 21.9, 19.3 ppm; LRMS (EI): $m/z$ 330 ($M^+$, 5), 286 (4), 285 (7), 270 (10), 269 (29), 268 (91), 255 (6), 254 (21), 253 (100); HRMS (EI): calcd for $C_{22}H_{34}O_2$ ($M^+$) 330.2553, found 330.2549; $[\alpha]_D^{20}=+48.3$ ($c$=0.06, $CHCl_3$).

Synthesis of **2:** To **23** (0.0013 g, 0.0039 mmol) was added HCl (600 μL) in *i*PrOH (2 drops of concentrated HCl in 10 mL *i*PrOH). After heating at 65 °C for 6 h, the crude mixture was concentrated in vacuo, and the residue was loaded on to silica gel directly and purified by flash chromatography using 5% EtOAc/Hexane to afford **2** (0.0008 g, 71% yield) as a colorless oil. **2**: $R_f$ (10% EtOAc in hexane) 0.53; IR ($CH_2Cl_2$): $\tilde{\nu}$=3597, 2960, 2928, 2869, 2854, 1100, 865 cm$^{-1}$; $^1$H NMR (500 MHz, $C_6D_6$): $\delta$=5.55 (br, s, 1H), 5.48 (dd, $J$=9.4, 4.6 Hz, 1H), 4.78 (s, 1H), 4.61 (s, 1H), 3.26 (dd, $J$=15.2, 4.2 Hz, 1H), 2.61 (ddd, $J$=13.2, 12.6, 6.0 Hz, 1H), 2.43 (sept, $J$=6.8 Hz, 1H), 2.23 (d, $J$=17.0 Hz, 1H), 2.08–2.15 (m, 2H), 2.03 (d, $J$=14.6 Hz, 1H), 1.96 (d, $J$=12.7 Hz, 1H), 1.51–1.62 (m, 3H), 1.47 (d, $J$=14.8 Hz, 1H), 1.40 (s, 3H), 1.25–1.36 (m, 1H), 1.14 (d, $J$=6.8 Hz, 3H), 1.12 (d, $J$=6.8 Hz, 3H), 0.93 ppm (s, 3H); $^{13}$C NMR (125 MHz, $C_6D_6$): $\delta$=154.8, 154.5, 150.4, 125.4, 115.4, 108.9, 79.5, 51.5, 46.1, 43.9, 42.0, 37.8, 35.7, 32.7, 27.9, 26.3, 24.1, 22.8, 22.6, 20.2 ppm; LRMS (EI): $m/z$ 286 ($M^+$, 39), 268 (100), 253 (93); HRMS (EI): calcd for $C_{20}H_{30}O$ ($M^+$) 286.2291, found 286.2286; $[\alpha]_D^{20}=-191$ ($c$=0.04, $CHCl_3$).

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**Keywords:** carbenes · cascade reaction · natural products · rhodium · total synthesis

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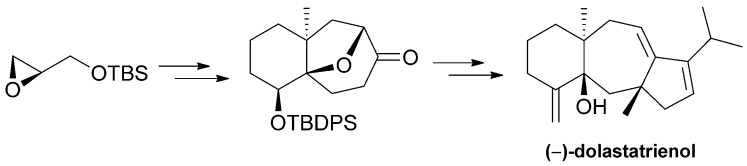


(−)-dolastatrienol

**Total Synthesis**

*Lai To Leung, Pauline Chiu**

■■ – ■■

**Total Synthesis of (−)-Dolastatrienol**

VIP

**Her name was Dola, she was a statrienol**: The asymmetric total synthesis of the diterpenoid (−)-dolastatrienol has been accomplished using a rhodium(II)-catalyzed carbene cyclization cycloaddition cascade reaction and an intramolecular Heck reaction as the key steps to furnish the tricyclic skeleton.