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Cyclic 1,2-Diketones as Core Building Blocks: A Strategy for the Total Synthesis of (−)-Terpestacin

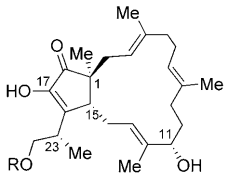
Barry M. Trost,* Guangbin Dong, and Jennifer A. Vance[a]

Abstract: We report a full account of our work towards the total synthesis of (−)-terpestacin (**1**), a sesterterpene originally isolated from fungal strain *Arthrinium* sp. FA1744. Its promising anti-HIV and anti-cancer activity, as well as its novel structure, make terpestacin an attractive synthetic target. A strategy based on the unique reactivity of cyclic 1,2-diketones (diosphenols) was developed and total synthesis of **1** was achieved in 20 steps, in the longest linear sequence, from commercially available 2-hydroxy-3-methyl-2-cyclopenten-1-one. The key feature of our synthesis is the double usage of a "Pd AAA-Claisen" protocol (AAA = asymmetric allylic alkylation), first in the early stages to generate the C1 quaternary center and then in the late stages to install the side chain. In addition, a rather unusual ene-1,2-dione moiety was synthesized and utilized as an excellent Michael acceptor to attach the C15 substituent. Several possible routes towards the total synthesis have been examined and carefully evaluated. During our exploration many interesting chemoselectivity issues have been addressed, such as a highly selective ring-closing metathesis and a challenging oxidation of a disubstituted olefin in the presence of three trisubstiuted ones.

Keywords: alkylation · asymmetric catalysis · Claisen rearrangement · terpenoids · total synthesis

Introduction

Isolation and biology: In 2007, the World Health Organization estimated that 30.6–36.1 million people worldwide were living with HIV and 2.1 million people had died of AIDS that year.[1] Over the past two decades significant effort has been applied to identifying pathological targets for HIV and exploring new drug candidates for its chemotherapy. One important target for finding treatments for HIV infection is syncytium formation, which constitutes a major cause of the death of human T4 cells.[2] During the screening for syncytium formation inhibitors in 1993, an attractive natural product named terpestacin (**1**) was found in fungal strain *Arthrinium* sp. FA1744 by a collaboration between Oka and Bristol-Myers Squibb.[3] Terpestacin was shown to effectively inhibit the formation of syncytia (giant-multinucleated cells that are caused by the expression of gp120 on cell surfaces during HIV infection),[3a] and its IC_{50} value is as low as 0.46 μg mL^{-1}, which suggests that it could be a promising drug lead in anti-HIV chemotherapeutics.[3a] Recently, terpestacin has also been isolated from other fungal sources such as *Ulocladium*[4] and *Bipolaris sorokiniana*.[5]



R = H; Terpestacin(**1**)
R = Ac; Fusaproliferin(**2**)

A recent oncological study shows that, both in vitro and in vivo, terpestacin is also able to inhibit angiogenesis without affecting endothelial cell viability and inhibits extracellular signal-regulated kinase activity in the cells.[6] This result implies that terpestacin could be employed for the treatment of cancer.

Structure: Besides these stimulating biological properties, the structure of terpestacin has been attractive to the synthetic community. Terpestacin contains a *trans*-fused [3.0.13]bicyclic skeleton that includes a 15-membered macrocycle with three geometrically defined trisubstituted olefins. Furthermore, it contains an uncommon diosphenol functionality (a cyclic 1,2-diketone with one ketone existing as an enol) within a heavily substituted five-membered ring. Interestingly, the structure of terpestacin contains a 4+4+4 combination that includes four oxygen atoms, four carbon–

[a] Prof. B. M. Trost, G. Dong, J. A. Vance
Department of Chemistry, Stanford University
Stanford, California 94305-5080 (USA)
Fax: (+1) 6507250002
E-mail: bmtrost@stanford.edu

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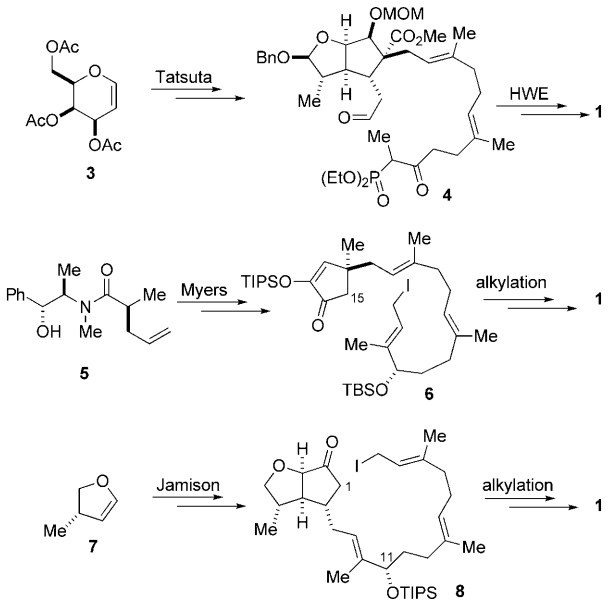
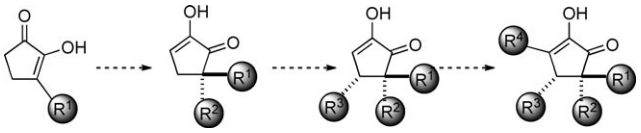
carbon double bonds, and four stereogenic centers, one of them quaternary. All of these features have posed significant challenges for the total synthesis of terpestacin.

Previous efforts: Given its promising anti-HIV and anticancer activities, along with its novel architecture, several elegant total syntheses of terpestacin have been reported to date. In 1998, Tatsuta et al. described the first racemic synthesis of **1**[7] and, later that year, they also reported the first enantioselective synthesis, starting from tri-*O*-acetyl-D-galactal **3** and using a selective Horner–Wadsworth–Emmons (HWE) reaction to close the macrocycle of the intermediate-compound **4** (Scheme 1).[8] The Myers group, in 2002,



Scheme 1. Previous enantioselective total syntheses of terpestacin (**1**); MOM = methoxymethyl, Ac = acetyl, Bn = benzyl, TIPS = triisopropylsilyl, TBS = *tert*-butyldimethylsilyl.

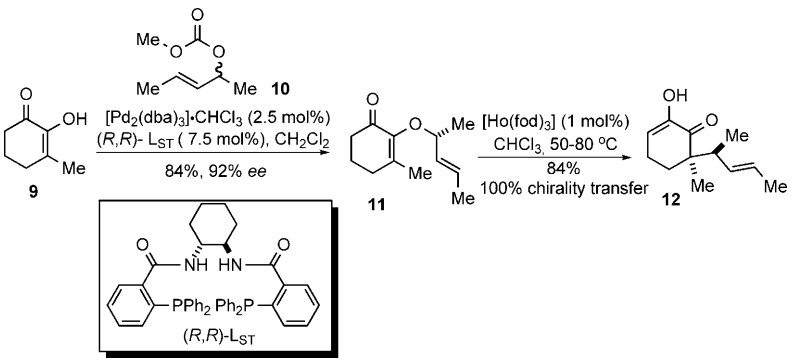
completed the second enantioselective synthesis of terpestacin, as well as a closely related natural product fusaproliferin (**2**).[9] They initiated their synthesis with pseudoephedrine-derived chiral amide **5** and constructed the macrocycle through a stereoselective alkylation of **6** at the C15 position. Moreover, this synthesis unambiguously established the absolute configuration of this natural product. In 2003, Jamison reported the third enantioselective synthesis starting from chiral dihydrofuran **7**, in which they discovered that siccanol is not 11-*epi*-terpestacin, but terpestacin itself. Jamison's synthesis features a highly selective, Ni-catalyzed, reductive coupling to afford the chiral allylic alcohol motif at C11 and a subsequent alkylation at the C1 position of **8** to provide the desired macrocycle.[10] Very recently, another racemic synthesis of **1** was completed by the Tius group, who employed an allene ether Nazarov reaction as a key step to construct the five-membered ring core and a HWE reaction to close the macrocycle.[11] In this article, we describe a full account of our work towards the enantioselective total synthesis of (−)-terpestacin, as well as a journey to the development of a unique strategy to stereoselectively and programmatically alkylate 3-substituted cyclopentane-1,2-diketones (Scheme 2).[12]



Scheme 2. Programmatic alkylation of cyclic 1,2-diketones.

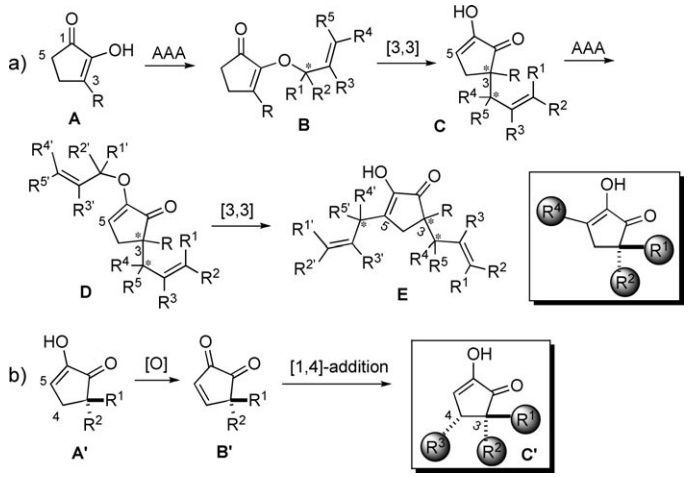
Diosphenols: Cyclic 1,2-diketones with one of the ketones in an enol form have been named diosphenols due to their similar reactivity to phenols.[13] Notably, 3-substituted cyclic 1,2-diketones exist as a single tautomeric species, which raises the attractive prospect of diosphenols serving as a pivotal core onto which several carbon-chain substituents can be installed in a stereoselective fashion. As with phenols, the enol OH of cyclic 1,2-diketones exhibits substantial nucleophilicity and, generally, only *O*-alkylation occurs when they are treated with alkylating agents.[14] In 2000, Trost and Schroeder developed an asymmetric allylic alkylation (AAA) method using diosphenols as nucleophiles and *O*-allylated products were obtained with high enantioselectivity (as in the reaction of **9** with **10** to form compound **11**; Scheme 3).[15] Subsequent Claisen-rearrangement of these AAA adducts then provided the *C*-alkylation products with excellent chirality transfer (as in the formation of **12** from **11**).

Basic principle: This *O*-allylation, Claisen rearrangement sequence should provide a chemo- and regioselective enolate



Scheme 3. Pd-catalyzed AAA-Claisen rearrangement sequence; DBA = dibenzylideneacetone, FOD = 6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionate.

allylation that can be performed asymmetrically with respect to the enolate, the allyl fragment, or both (Scheme 4, a). During this transformation up to two stereogenic centers



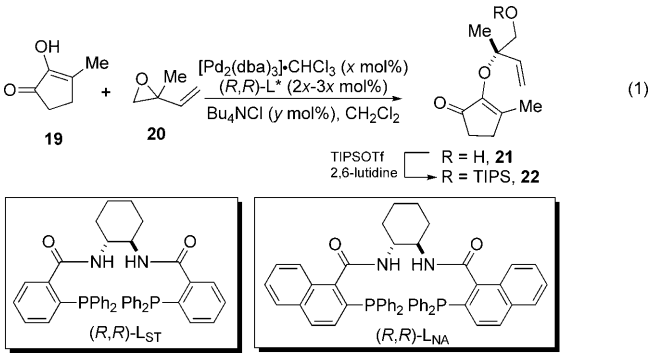
Scheme 4. Basic principle: the controlled substitution of cyclic 1,2-diketones to enable the synthesis of terpestacin (**1**).

can be created, including all-carbon quaternary ones. Moreover, the Claisen rearrangement product (**C**) regains diosphenol functionality that can be used as a substrate in the same sequence again to introduce another alkyl substituent at the C5 position. On the other hand, oxidation of 3,3-disubstituted diosphenol **A′** could provide a relatively unknown, but highly electrophilic, cyclopentenedione species, **B′** (Scheme 4, b). Conjugate addition of alkyl nucleophiles across **B′** should install a third carbon chain at the C4 position. Therefore, we envision that all the carbon substituents on the five-membered-ring core of terpestacin could be programmatically introduced in a chemo-, regio-, and stereoselective manner.

Results and Discussion

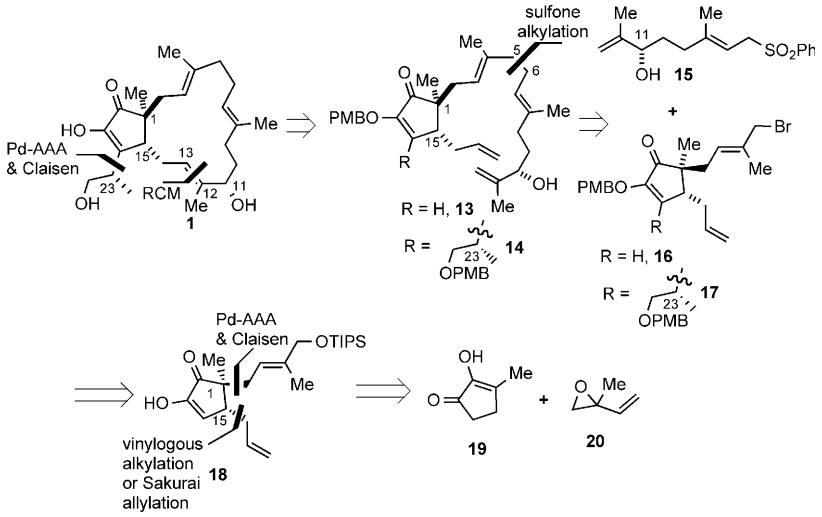
Synthesis plan: From a retrosynthetic viewpoint (Scheme 5), we envisaged that the side chain and the C23 stereocenter would be accessed through the "Pd AAA-Claisen" protocol followed by oxidative alkene cleavage and the 15-membered macrocycle could be constructed by a highly selective ring-closing metathesis (RCM) to form the C12–C13 olefin. The RCM precursors **13** or **14** could be formed by alkylation of sulfone **15** with the corresponding allyl bromides (**16** or **17**), which could ultimately be derived from diosphenol **18**. The C15 stereocenter of **18** could be generated either by a vinylogous enolate alkylation, or through a stereoselective Sakurai allylation of the corresponding enone and the C1 quaternary center would arise from another "Pd AAA-Claisen" reaction of the inexpensive and commercially available 3-methyl-1,2-cyclopentanedione **19** and isoprene monoepoxide **20**.

Pd-catalyzed AAA reactions between diosphenol 19 and isoprene monoepoxide 20 [Eq. (1)]:



(1)

Initial attempts to effect the AAA reaction between **19** and **20** by using the published reaction conditions[15] gave only moderate enantioselectivity (Table 1, entries 1 and 2). Note that tetrabutylammonium chloride was employed as an additive to promote the π–σ–π equilibration required for resolution of vinyl epoxide **20** (Scheme 6). In this case, the naphtho-Trost ligand (L_{NA}) gave slightly higher *ee* (Table 1, entry 2; 57% *ee*) than the standard ligand (L_{ST}) (Table 1, entry 1, 48% *ee*). Lowering the catalyst loading from 2.5 to 0.5 mol% did not hamper the yield; on the contrary, the enantioselectivity increased from 57 to 67% *ee* (Table 1, en-

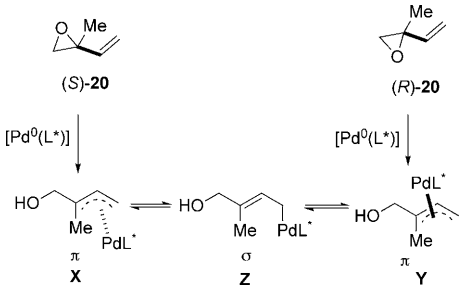


Scheme 5. Retrosynthetic analysis; PMB = *para*-methoxybenzyl.

Table 1. Selected optimization studies.[a]

Entry	L[b]	x[b]	y[b]	t [h]	T [°C]	c [M]	Yield [%][c]	ee [%][d]
1	L_{ST}	2.5	30	1.0	40	0.05	72	48
2	L_{NA}	2.5	30	1.0	40	0.05	85	57
3	L_{NA}	0.8	35	1.0	40	0.05	79	66
4	L_{NA}	0.5	30	0.3	40	0.05	88	67
5	L_{NA}	0.5	50	1.0	40	0.05	83	74
6	L_{NA}	0.5	30	0.3	RT	0.05	79	66
7	L_{NA}	0.5	30	0.3	60	0.05	85	67
8	L_{NA}	0.5	50	2.5[e]	40	0.08	94	90
9	L_{ST}	2.0	50	6.0[e]	RT	0.07	93–95[f]	88–96

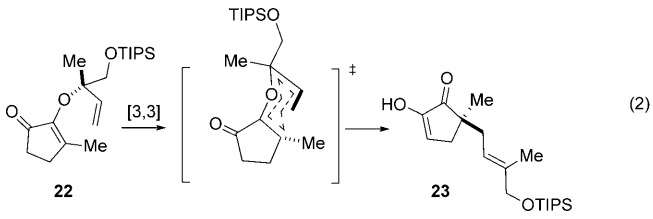
[a] The reaction was operated with 2 equivalents of **20** and 1 equivalent of **19**. [b] See Equation (1) for definitions of L, x, and y. [c] Isolated yield. [d] Enantioselectivities were determined for the acetate derivatives by chiral HPLC. [e] A solution of **19** was added slowly through a syringe pump over the indicated amount of time. [f] Isolated yield after direct conversion to TIPS ether **22**.



Scheme 6. π–σ–π Equilibration.

tries 2 and 4). Raising the loading of chloride salt caused a slight but noticeable increase on the enantioselectivity (Table 1, entry 5). Further study suggested that temperature did not play an important role on either the yield, or the enantioselectivity (Table 1, entries 6 and 7). Under all the test conditions the reaction was observed to proceed at an extremely high rate. A high reaction rate with low *ee* suggests that the π–σ–π interconversion between the two diastereomeric palladium–π-allyl species **X** and **Y** (see Scheme 6) is relatively slow compared with the nucleophilic attack. Thus, by decreasing the nucleophile concentration, the rate of nucleophilic addition should be lowered, allowing the palladium–π-allyl intermediates (**X** and **Y**) enough time to equilibrate, which should provide a high facial selectivity. Indeed, slow addition of **19** through a syringe pump dramatically improved the enantioselectivity to 90% *ee* (Table 1, entry 8). From these studies emerged the most practical set of conditions and, as shown in Table 1, entry 9, up to 96% *ee* could be achieved with the standard Trost ligand. Pd-AAA adduct **21** was subsequently protected in the same pot with a bulky TIPS (TIPS = triisopropylsilyl) group, and the silylated product **22** was isolated in 93–95% yield.

Claisen rearrangement leading to *C*-alkylated product 23: With AAA adduct **22** in hand, the stage was set for a Claisen rearrangement to transfer the chirality from the side chain onto the ring [Eq. (2)].



(2)

The compound [Ho(fod)$_3$] (fod = heptafluorodimethyloctanedione) has been established as an excellent catalyst for such rearrangements.[15] Indeed, treatment of TIPS ether **22** with 10 mol% [Ho(fod)$_3$] in chloroform at 35–45 °C for five days did provide the rearranged product **23** in 20% yield (Table 2, entry 1). The *E/Z* selectivity for the newly formed

Table 2. Selected optimization of the [3,3]-Claisen rearrangement reaction.

Entry	Additives (10 mol%)	Solvent	T [°C]	t [h]	Yield [%][a]	E:Z[b]
1	[Ho(fod)$_3$]	$CHCl_3$	35–45	120	20	4.1:1
2	[Eu(fod)$_3$]	$CHCl_3$	35	360	N/A[c]	N/A
3	[Ho(fod)$_3$]	$CHCl_3$	55	40	33	5.8:1
4	none	$CHCl_3$	55	40	50	6.3:1
5	none	$CHCl_3$	45	120	37	8.3:1
6	none	none	70	20	89	4.8:1
7	none	$CHCl_3$	100[d]	0.25	82–93	4–5:1
			120[d]	0.25		
8	[Ho(fod)$_3$]	$CHCl_3$	100[d]	0.25	74	5.0:1
			120[d]	0.25		
9	[Ho(tmhd)][e]	$CHCl_3$	100[d]	0.25	34	4.0:1
			120[d]	0.25		
10	none	purified $CHCl_3$	100[d]	0.25	N/A[c]	N/A
			120[d]	0.25		
11	none	DME	160[d]	3	100[f]	2.7:1

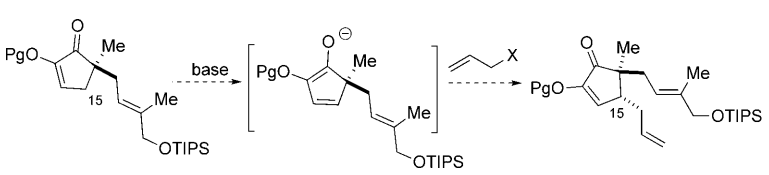
[a] Isolated yield. [b] Determined by ^{1}H NMR spectroscopy. [c] Incomplete conversion with byproduct formation. [d] Microwave heating. [e] TMHD = 2,2,6,6-tetramethyl-3,5-heptanedionate. [f] Complete conversion.

alkene geometry in **23** was 4.1:1 (determined by ^{1}H NMR spectroscopy), favoring the *E* isomer. Use of the related [Eu(fod)$_3$] as the catalyst, however, gave incomplete conversion and the formation of unidentified byproducts (Table 2, entry 2). When warmed to 55 °C for 40 h, diosphenol **23** was afforded in 33% yield and 5.8:1 *E/Z* selectivity (Table 2, entry 3). Surprisingly, in the absence of the catalyst, this sigmatropic rearrangement proceeded equally well, or even slightly better, by simply heating **22** in a minimal amount of chloroform (Table 2, entry 4). An increased *E/Z* ratio (8.3:1) was observed when **22** was heated at a reduced reaction temperature (45 °C); however, the reaction rate was significantly diminished (Table 2, entry 5). In the absence of a solvent, this Claisen rearrangement occurred with increased yield (89%) and reasonably good *E/Z* selectivity (4.8:1), although a long period of heating (70 °C, 20 h) was still required to allow the reaction to go to completion (Table 2, entry 6). A more practical protocol was then developed as shown in Table 2, entry 7. Replacement of conventional

heating with microwave irradiation (100 °C for 15 min followed by 120 °C for 15 min) significantly increased the reaction rate and the product (**23**) was isolated in 82–93 % yield. Attempts to enhance the *E/Z* selectivity by employing the Lewis acid catalysts [Ho(fod)$_3$] and [Ho(tmhd)] (H-tmhd = 2,2,6,6–tetramethylheptane-3,5–dione) proved to be unfruitful (Table 2, entries 8 and 9).

It should be noted that the choice of chloroform as the solvent is not arbitrary. When 1,2-dimethoxyethane (DME) was used as solvent, a 3 h microwave heating reaction at 160 °C was required and the *E/Z* selectivity of the product was lower (2.7:1, Table 2, entry 11). Interestingly, under the same conditions as in Table 2, entry 7, but utilizing chloroform freshly distilled from K_2CO_3, the Claisen rearrangement failed to give full conversion and the product was contaminated with unidentified byproducts (Table 2, entry 10). We hypothesized that a trace amount of water and HCl present in "unpurified" chloroform may help to catalyze this [3,3]-sigmatropic rearrangement. In the case of the solvent-free conditions, the diosphenol product itself can act as the acid catalyst due to the acidity of the enol OH. Chirality transfer from **22** to **23** proved to be complete and, at this point, the absolute configuration of **23** was tentatively assigned in analogy with our previous work.[15]

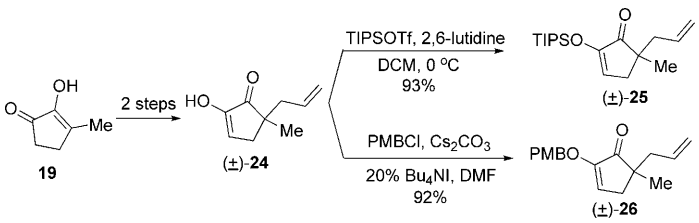
Installation of the allyl group at the C15 position (terpestacin numbering): Elaboration of diketone **23** to the natural product requires installation of an allyl side chain at the C15 position. One possible route to this compound is to generate a vinylogous enolate by deprotonation of a protected diketone followed by quenching with an allylic electrophile [see Eq. (3) in which Pg = protecting group].



(3)

To that end, a model system was employed to examine the feasibility of this method. Model substrate (±)-**24** was prepared in 88 % yield over two steps from diosphenol **19**.[14] Subsequent TIPS or *p*-methoxybenzyl (PMB) protection of the enol provided the corresponding silyl ether (±)-**25** and benzyl ether (±)-**26** in excellent yield (Scheme 7). However, treatment of both (±)-**25** and (±)-**26** with various bases and electrophiles in different solvents failed to provide any of the desired alkylation products. Instead, some *O*-alkylation byproducts and decomposition of the starting material were observed, which can likely be attributed to the fragileness of the vinylogous enolate intermediate.

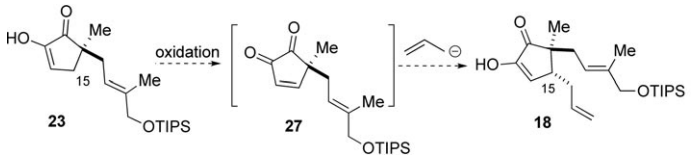
Alternatively, an umpolung strategy can be envisioned. Instead of using the diosphenol as a nucleophile, oxidation of the diketone would create a "hot" electrophile, an ene-



Scheme 7. Synthesis of the model substrates.

dione (**27**), which allows an allylic nucleophile to attack at the C15 position as shown in Equation (4). Conjugated cyclopentene-1,2-diones containing no substituents at C3 or C4, such as **27**, are a rare and underutilized species[16] about which limited chemistry is known. The reaction of the model system, TIPS enol ether (±)-**25**, under Corey-modified Saegusa oxidation conditions[17] resulted in a messy reaction mixture and incomplete conversion [as shown in Eq. (5) in which TBHP = *tert*-butyl hydroperoxide]. 2-Iodoxybenzoic acid (IBX) oxidation[18] of the unprotected model diketone (±)-**24** gave none of the desired enedione compound, but caused decomposition of the starting material [as shown in Eq. (6) in which MPO = *p*-methoxypyridine-*N*-oxide].

After extensive experimentation, we found that treatment of (±)-**24** with 1 equivalent of palladium acetate and 1.5 equivalents of cesium carbonate in acetonitrile at ambient temperature cleanly provided cyclopentene-α-dione (±)-**28** as a yellow oil, in 78 % yield (Scheme 8). To the best of our knowledge, this represents the first example of direct Saegusa oxidation of unprotected diosphenols.[19] Surprisingly, this enedione compound is relatively stable towards aque-



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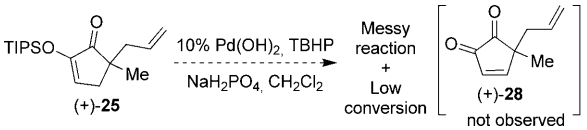
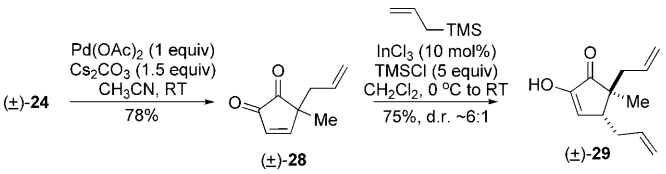


(5)

(6)

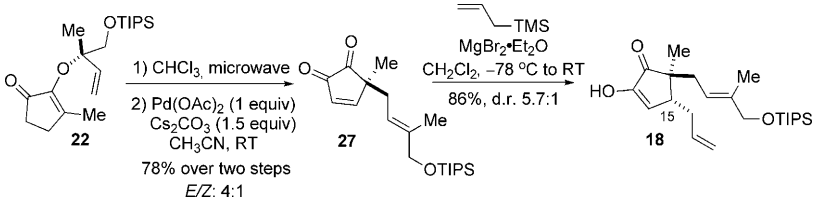
ous workup and silica gel chromatography. Attempts to reduce the amount of palladium required were, unfortunately, unfruitful. For example, using



Scheme 8. Model reactions for allylation at the C4 position of diosphenol 24; TMS = trimethylsilyl.

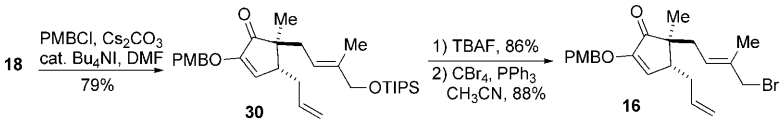
molecular O_2 (in DMSO), benzoquinone, or $Cu(OAc)_2$ as the stoichiometric oxidant failed to turn over the Pd catalyst. A subsequent indium-catalyzed Sakurai allylation[20] was then employed and the allyl group was installed into (±)-**28** in a diastereoselective fashion. Diosphenol (±)-**29** was isolated in 75% yield, as a 6:1 mixture of isomers. In the major diastereomer the two allyl groups are in a *trans*-position relative to each other, which was determined by 1D nOe experiments. Moreover, this transformation constitutes the first example of an intermolecular C-1,4-addition into this type of enedione species.[21]

With successful installation of an allyl substituent at the C4 position in the model system, we tested these conditions on the real system. Treatment of the Claisen rearrangement product generated from **22** under the newly developed Saegusa oxidation conditions smoothly gave cyclopentene-α-dione **27** in 78% yield over the two steps (Scheme 9). For the subsequent allylation, although indium chloride was used as the Lewis acid in the model system, the use of magnesium bromide was more effective for the real system. Allylation product **18** was isolated in 86% yield with 5.7:1 d.r.; the relative stereochemistry and the d.r. were determined by 1D nOe experiments and ^{1}H NMR spectroscopy, respectively.

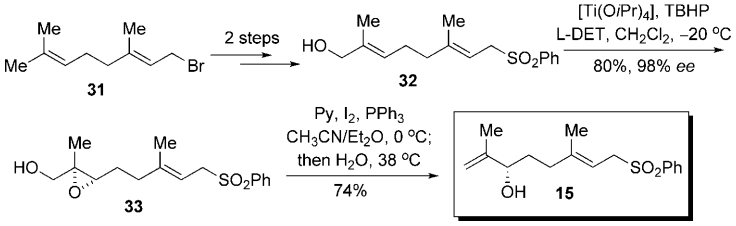


Scheme 9. Synthesis of diosphenol **18**.

An RCM approach to constructing the 15-membered carbocycle: Next, the enol OH in diosphenol **18** was protected as a PMB ether (**30**; Scheme 10). Subsequently, the TIPS protecting group was removed by using TBAF and treatment of the resulting allyl alcohol with PPh_3 and CBr_4 provided allyl bromide segment **16** in high yield.



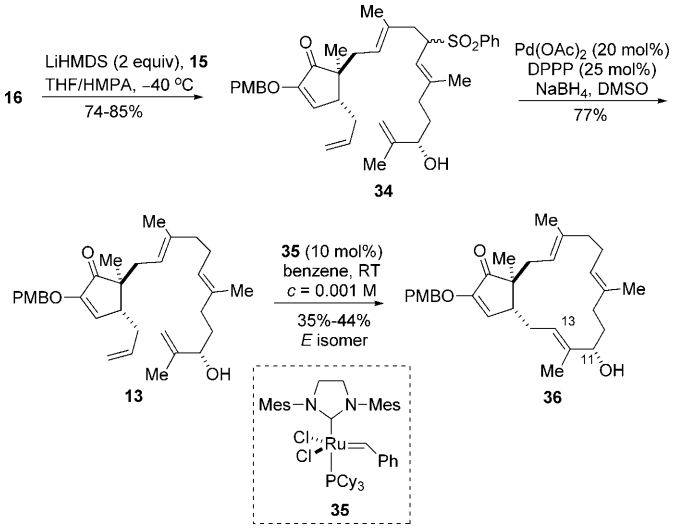
Scheme 10. Synthesis of allyl bromide **16**; TBAF = tetrabutylammonium fluoride.



Scheme 11. Synthesis of sulfone fragment **15**; Py = pyridine, L-DET = L-diethyl tartrate

The synthesis of sulfone segment **15** is depicted in Scheme 11. Commercially available geranyl bromide (**31**) was used to prepare known allyl alcohol **32** two steps.[22] Under Sharpless asymmetric epoxidation conditions allyl alcohol **32** was converted to chiral epoxide **33** with 98% *ee*. A reductive epoxide rearrangement procedure was then adopted from Li et al.;[23] the epoxy alcohol was converted in situ into the corresponding epoxy iodide with PPh_3, iodine, and pyridine, which upon addition of water underwent reductive elimination of the iodide ion that is formed to afford chiral allyl alcohol **15** in 74% yield.

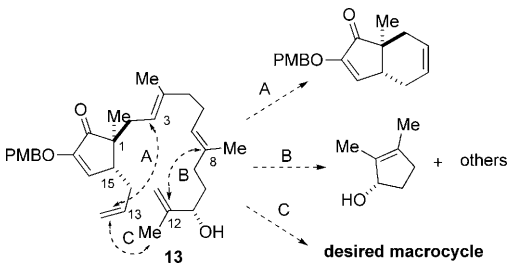
With compounds **15** and **16** in hand, the stage was set to couple these two fragments together. After careful optimization, treatment of a mixture of **15** and **16** with 2 equivalents of LiHMDS in THF-HMPA at −40 °C cleanly provided coupling product **34**, in very good yield, as a 1:1 mixture of diastereomers (Scheme 12). Notably, protection of the allylic alcohol is not necessary and no *O*-alkylation product was isolated. The choice of base seems to be critical; for example, use of NaHMDS or KHMDS was much less effective than LiHMDS. Solvent and temperature optimization studies revealed that a THF/HMPA (3:1) mixed solvent and −40 °C combination gave the best yield. A number of sulfone removal methods were then attempted, and a Pd-catalyzed reductive desulfonylation turned out to be the most efficient method for substrate **34**. By using $Pd(OAc)_2$–DPPP (1,3-bis(diphenylphosphino)propane) as the catalyst and $NaBH_4$ as the stoichiometric reductant in DMSO, this desulfonation proceeded with high regioselectivity, almost no loss of olefin geometry, and RCM precursor **13** was furnished in 77%



Scheme 12. Synthesis of macrocycle **36**; HMDS = hexamethyl disilazide, Cy = cyclohexyl, Mes = mesityl, HMPA = hexamethylphosphoramide, DPPP = 1,3-bis(diphenylphosphino)propane.

yield. It is worth noting that carefully dried DMSO (distilled over CaH_2, then stored over 4 Å molecular sieves) was required for this desulfonylation reaction.

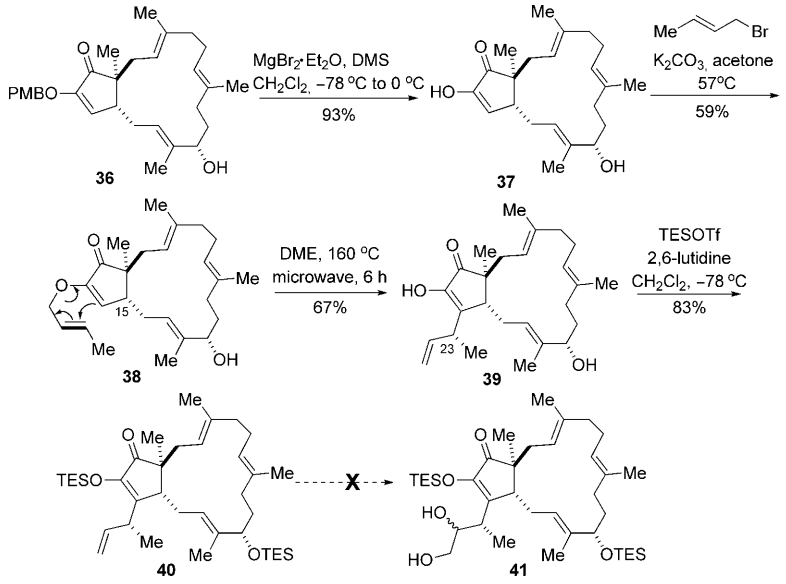
Since compound **13** contains five olefins, many outcomes are possible for the following RCM reaction (Scheme 13). For example, C13 and C3 could close to form a six-membered ring (pathway A), C8 and C12 could close to form a five-membered ring (pathway B), and so forth. After careful screening, we found that treatment of **13** with 10 mol% of Grubbs second-generation catalyst (**35**, see Scheme 12)[24] in benzene at room temperature produced the desired 15-membered carbocycle **36** in a reasonably good yield[25] (35–44% of the *E* isomer).[26] We also found that having the C11 hydroxyl group protected with a TBS group did not provide any 15-membered ring product, which indicates that the free allylic alcohol moiety could be critical for the success of this challenging RCM. We rationalize that coordination of the hydroxyl group with the ruthenium catalyst, or potential intramolecular hydrogen bonding between the OH and the diketone moiety might be key factors in the formation of the macrocycle. Benzene was selected as the solvent for this RCM reaction instead of dichloromethane, because a less polar solvent would be beneficial for the intramolecular hydrogen bonding. In addition, a low reaction temperature proved to be important, as various byproducts formed at elevated temperatures. Moreover, the use of the less reactive Grubbs first-generation catalyst[27] failed to provide any macrocyclization product.



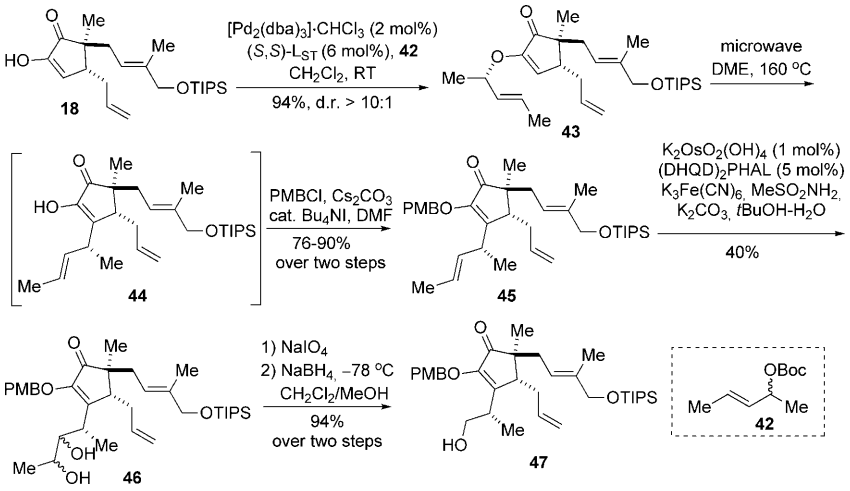
Scheme 13. Possible RCM pathways.

Initial approach to installing the side chain: The advancement of bicycle **36** to terpestacin (**1**) requires installation of a side chain at C16, along with the C23 stereogenic center. Removal of the PMB group in **36** turned out to be nontrivial. A large number of methods for PMB deprotection, such as 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, trifluoroacetic acid, ceric ammonium nitrate, BF_3, and so forth, proved unsuccessful. In the end, a relatively unconventional method was tried by using $MgBr_2$ and dimethyl sulfide (DMS).[28] We anticipated that the chelation of Mg^{2+} to both the enol ether and the ketone could facilitate the subsequent debenzylation, either by the bromide or DMS present. Indeed, under these conditions the PMB group was cleanly removed in excellent yield (Scheme 14). We envisioned that, due to control by the adjacent C15 stereocenter, the Claisen rearrangement of the *O*-crotylated diosphenol **38** should give the *C*-alkylation product with the desired stereochemistry. Indeed, treatment of **37** with *trans*-crotyl bromide and potassium carbonate, followed by microwave heating in DME provided adduct **39** containing the whole carbon framework and all the stereocenters present in the natural product.[29] At this point, the stereochemistry of the newly formed C23 center in **39** was tentatively assigned as that shown in Scheme 14. The enol and the allylic alcohol were subsequently protected with TES (TES = triethylsilyl) groups in one step. All efforts to selectively oxidize the terminal olefin in compound **40** without touching any of the three trisubstituted alkenes to form **41** remained unfruitful. For example, under regular dihydroxylation or diboration/oxidation conditions[30] a complex mixture was obtained without any of the desired product. This result implies that the chemoselective oxidation of the terminal olefin over the trisubstituted olefins is very challenging considering that the latter are typically more susceptible to oxidation.

Alternate route: a second Pd AAA-Claisen sequence to install the side chain before the macrocyclization: Given the difficulties discovered in cleaving the alkene in the side chain at a very late stage, an alternate route is to furnish the side chain first and then close the macrocycle at the very end. Furthermore, instead of dealing with a less electron-rich terminal olefin, installation of a disubstituted alkene should significantly increase the chance of the desired oxidative cleavage of the side chain. To this end, a second Pd-catalyzed AAA reaction between diosphenol **18** and allyl carbonate **42** using the standard (*S*,*S*)-Trost ligand ((*S*,*S*)-L_{ST}) provided *O*-allylated product **43** in 94% yield with over 10:1 diastereoselectivity, which was determined by ^1H NMR spectroscopy (Scheme 15). The stereochemistry of the newly formed chiral center in **43** was assigned by analogy to other AAA reactions with allyl carbonate **42**.[15] Subsequent mi-



Scheme 14. Initial efforts to install the side chain in the presence of the macrocycle.

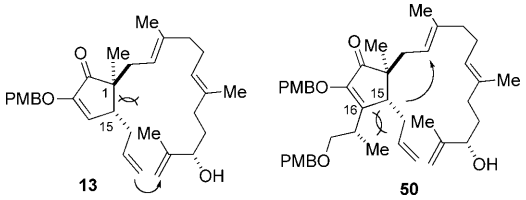


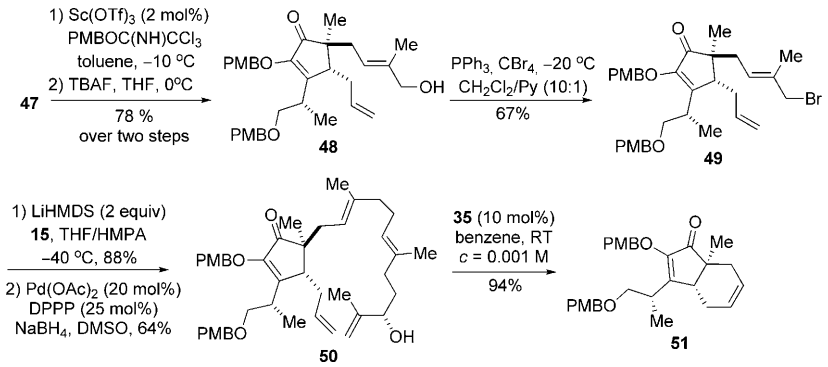
Scheme 15. Installation of the side chain before macrocyclization.

crowave-mediated Claisen rearrangement gave diosphenol **44**, which was then protected as a PMB ether. The resulting compound, **45**, contains various olefins: one mono-, one di-, and one trisubstituted olefin, as well as one tetrasubstituted conjugated enol ether. Thus, to selectively oxidize the disubstituted olefin in the presence of the others is a challenge. For example, treatment of **45** with *meta*-chloroperbenzoic acid only gave an epoxide at the position of the trisubstituted olefin. Fortunately, after extensive screening, the desired diol, **46**, was obtained in 40% (unoptimized) yield under Sharpless' asymmetric dihydroxylation conditions.[31] It is likely that the bulky $(DHQD)_2PHAL$ ligand (hydroquinidine 1,4-phthalazinediyl diether) would have unfavorable steric interactions with the TIPS group and the C1 quaternary center that result in slow oxidation of the trisubstituted alkene. Furthermore, the monosubstituted olefin is relatively electron-poor. These stereoelectronic biases could be the key factors which allow this chemoselective oxidation. Subsequent periodate cleavage of the diol followed by chemoselective reduction, in the presence of the ketone, of the aldehyde formed with $NaBH_4$ at −78 °C in a CH_2Cl_2/MeOH mixed solvent completed the construction of the side chain and gave **47**.

Scandium-catalyzed PMB protection of primary alcohol **47** followed by TBAF-mediated desilylation gave allylic alcohol **48** in 78% yield over two steps (Scheme 16). Treatment of **48** with PPh_3 and CBr_4 in a dichloromethane/pyridine mixed solvent[32] at −20 °C afforded allyl bromide **49**, which was then subjected to the sulfone-coupling and desulfonation conditions described previously. Adduct **50**, which is formed in this reaction, was isolated in 56% yield over the two steps and serves as the precursor for the subsequent RCM reaction. Unfortunately, treatment of **50** under the exact olefin metathesis conditions disclosed earlier for substrate **13** failed to provide any of the macrocycle products. Instead, *trans*-fused [3.0.4] bicycle **51** was obtained in 94% yield as the only product from the RCM reaction.

Why did substrates **13** and **50** (depicted here together) give totally different reactivity in the RCM reaction? We rationalize that the major steric interaction in the core of **13** is between the C15 allyl group and the two substituents at the C1 quaternary stereocenter. This interaction would likely push the two groups away from each other, which ultimately results in a favorable macrocyclization. However, in compound **50**, the C1–C15 interaction is compromised by a strong repulsion between the C15 allyl group and the C16 side chain. Moreover, formation of a six-

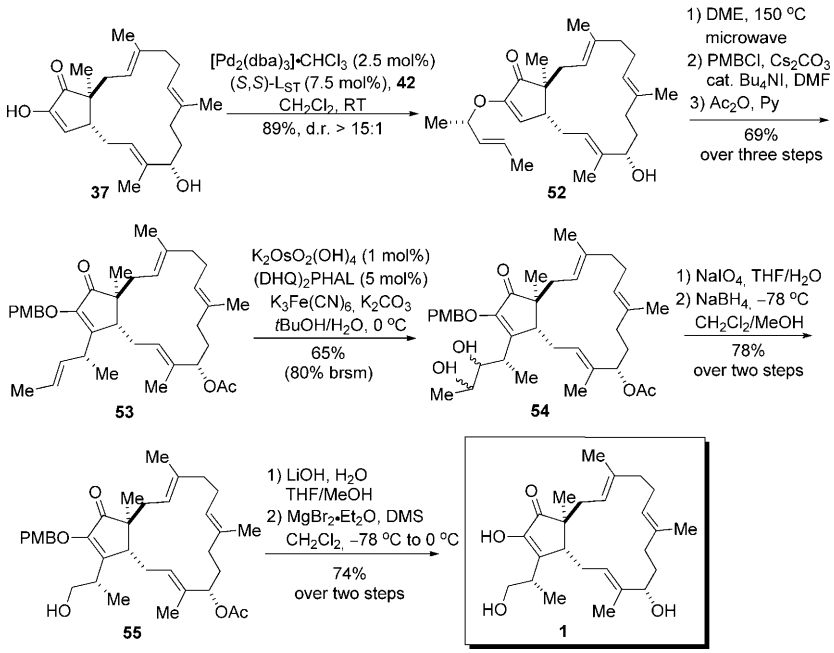




Scheme 16. Unsuccessful macrocyclization.

membered ring is thermodynamically favored. Thus, all these factors led to the preferred cyclization of compound **50** being to form the six-membered ring in lieu of a macrocyclization.

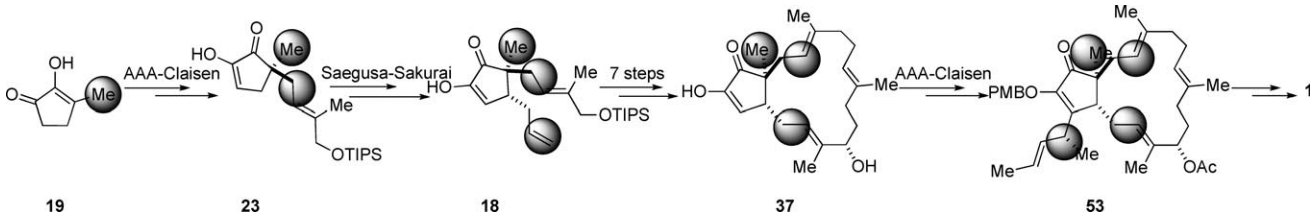
Revised approach leading to the total synthesis of (1): Encouraged by the success of the macrocycle formation in the first route and the success of the side chain installation in the second pathway, we decided to combine the merits of both approaches and further revise the method. We envisioned that a similar approach to that used in the second route could be applied to installing the side chain onto macrocycle **37** (Scheme 17). Indeed, application of the AAA-Claisen rearrangement sequence to diosphenol **37** uneventfully formed the side chain containing a *trans*-alkene with excellent diastereoselectivity. Note that AAA adduct **52** was isolated as almost a single diastereomer, as determined by ^{1}H NMR spectroscopy,[33] and the stereochemistry of the newly formed stereocenter in **52** was assigned by analogy to similar AAA reactions with allyl carbonate **42**.[15] The diosphenol OH was then protected as a PMB ether. An acetyl group was selected as the protecting group for the allyl alcohol moiety, firstly, because it can be easily removed by hydrolysis and, secondly, because an electron-withdrawing group like acetate should deactivate the adjacent trisubstituted olefin to oxidation. With tetraene **53** in hand, the remaining challenge was to selectively cleave the 1,2-disubstituted olefin in the presence of the three trisubstituted olefins. Lessons learned from the second attempted synthetic route led us to explore the possibility of using the Sharpless asymmetric dihydroxylation reaction to solve this chemoselectivity issue. To our delight, treatment of **53** with AD-mix-α[34]/$CH_3SO_2NH_2$ gave the desired diol, **54**, in 65% (80% based on recovered starting material) yield, whereas the use of AD-mix β resulted in a much lower yield (24%).[35] We rationalized that the chemoselectivity of this reaction comes from the fact that the endocyclic trisubstituted olefins would have a facial bias owing to their restricted rotation, whereas the disubstituted olefin is more conformationally flexible. In addition, the crystal structure of terpestacin[3b] indicates that within the macrocycle the C3–C4 and C7–C8 olefins are oriented in a similar fashion. Therefore, by using an asymmetric oxidation that is mismatched for the trisubstituted alkenes, oxidation of the disubstituted olefin would be kinetically favored. Advancement of diol **54** to the natural product was then achieved in a straightforward manner. Periodate cleavage of the vicinal diol followed by reduction of the resulting aldehyde furnished compound **55** with the desired the side chain. Subsequent removal of the acetate and PMB protecting groups ultimately afforded (−)-terpestacin (**1**), which is spectroscopically identical to the compounds previously reported.[9,10]



Scheme 17. Total synthesis of (−)-terpestacin (**1**); DHQ = dihydroquinine.

Conclusion

As summarized in Scheme 18, a unique strategy has been developed for the enantioselective total synthesis of terpestacin (**1**)



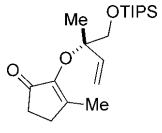
Scheme 18. Summary.

based on the unusual reactivity of diosphenols. By multiple usage of the α-diketone functionality, twice in the "Pd AAA-Claisen" protocol and once by the employment of its oxidized form, the ene-1,2-dione, stereoselective alkylation of cyclopentane-1,2-diketones could be achieved in a programmatically controlled fashion. An unusual procedure for direct oxidization of the diosphenol moiety to the ene-1,2-dione was developed and this enedione species proved to be an excellent Michael acceptor for a subsequent intramolecular 1,4-Sakurai allylation. The chemo- and regioselective desulfonylation of an allylic sulfone catalyzed by Pd^0 is also noteworthy. Several possible routes towards the total synthesis have been examined and carefully evaluated. During our exploration many interesting chemoselectivity issues have been addressed and discussed in detail, including a chemoselective RCM to form the 15-membered carbocycle and a dihydroxylation reaction to oxidize a disubstituted olefin in the presence of various other more electronically activated olefins. It is envisaged that this diosphenol-based strategy, along with the issues resolved in this work, will have the potential to shed new light on the total syntheses of related terpenoid natural products.

Experimental Section

Selected experimental procedures for the preparation of **22**, **27**, **18**, **34**, **13**, **36**, **52–55** and **1** (terpestacin) appear below. Full experimental details for all new compounds are given in the Supporting Information. The optical rotation measurements were taken at 22 °C.

Compound 22: (on a 3.6 mmol scale) In a flame-dried, argon-purged round-bottom flask $[Pd_2(dba)_3]\cdot CHCl_3$ (71.0 mg, 0.0685 mmol), (*R,R*)-L_{ST} (145.4 mg, 0.210 mmol), and Bu_4NCl (497.2 mg, 1.79 mmol) were combined and dissolved in dry, deoxygenated CH_2Cl_2 (100 mL). Isoprene monoepoxide (754 mg, 8.97 mmol) was added to this solution. The resulting yellow solution was stirred at room temperature for 15 min, at which time a solution of **19** (403.6 mg, 3.60 mmol) in dry, deoxygenated CH_2Cl_2 (50 mL) was slowly added by syringe pump, over 6 h. After completion of the slow addition, the reaction was cooled to −78 °C. 2,6-Lutidine (0.92 g, 8.95 mmol) and TIPSOTf (2.51 g, 8.18 mmol) were added and the solution was slowly warmed to room temperature, over 16 h. Concentration in vacuo and purification by flash column chromatography (petroleum ether/diethyl ether = 95:5, then 9:1) gave the product as a yellow oil (1.16 g, 93%, 96% *ee*. The *ee* of this sample was assumed to be the same as the *ee* of the acetate derivative prepared from a 1 mL aliquot of the unisolated, intermediate alcohol. The *ee* was determined by HPLC OC column, 1.0 mL min^{-1}, 90:10 heptane/isopropanol, t_r (major): 29.32 min, t_r (minor): 38.41 min).



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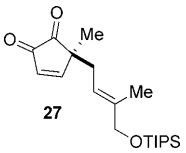
For a larger scale: (7.14 mmol) In a flame-dried, argon-purged round-bottom flask $[Pd_2(dba)_3]\cdot CHCl_3$ (140.9 mg, 0.136 mmol), (*R,R*)-L_{ST} (297.7 mg, 0.431 mmol), and Bu_4NCl (1.04 g, 3.73 mmol) were combined and dissolved in dry, deoxygenated CH_2Cl_2 (100 mL). Isoprene monoepoxide (1.50 g, 17.8 mmol) was added to this solution. The resulting yellow solution was stirred at room temperature for 15 min, at which time a solution of **19** (800.1 mg, 7.14 mmol) in dry, deoxygenated CH_2Cl_2 (100 mL) was slowly added by syringe pump, over 6 h. After completion of the slow addition, the reaction was cooled to −78 °C. 2,6-Lutidine (2.02 g, 18.9 mmol) and TIPSOTf (4.56 g, 14.9 mmol) were added and the solution was slowly warmed to room temperature, over 16 h. Concentration in vacuo and purification by flash column chromatography (petroleum ether/diethyl ether = 95:5, then 9:1) gave the product as a yellow oil (2.39 g, 95%, 88% *ee*). R_f: 0.46 (petroleum ether/ethyl acetate = 8:1); $[\alpha]_D$: +7.2 (*c* = 1.02 in CH_2Cl_2, in this case 88% *ee*); ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 6.05 (dd, *J* = 17.6, 10.9 Hz, 1H), 5.18 (dt, *J* = 17.6, 0.61 Hz, 1H), 5.12 (dq, *J* = 10.9, 0.61 Hz, 1H), 3.79 (s, 2H), 2.43–2.40 (m, 2H), 2.33–2.28 (m, 2H), 1.98 (d, *J* = 0.61 Hz, 3H), 1.37 (s, 3H), 1.07–1.02 ppm (m, 21H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 204.4, 161.1, 150.7, 140.3, 115.6, 83.7, 70.1, 32.5, 27.5, 20.4, 18.0, 17.7, 16.0, 11.9 ppm; IR (film): $\tilde{\nu}$ = 2943, 2866, 1749, 1714, 1640, 1463, 1410, 1384, 1333, 1247, 1204, 1096, 996, 882, 810 cm^{-1}; elemental analysis calcd (%) for $C_{20}H_{36}O_3Si$: C 68.13, H 10.29; found: C 68.36, H 10.10.

Compound 27: Compound **22** (1.468 g, 4.17 mmol) was transferred into a microwave vial with $CHCl_3$ (3 mL). The microwave vial was sealed and heated to 100 °C for 15 min, then 120 °C for 15 min. The $CHCl_3$ was removed under reduced pressure, the crude compound was then dissolved in CH_3CN (20 mL), and then Cs_2CO_3 (2.0 g, 6.26 mmol) and $[Pd(OAc)_2]$ (1.03 g, 4.59 mmol) were added. The resulting mixture was stirred at room temperature for 30 min. Palladium black was filtered out through a celite–silica gel cake and compound **27** was purified by silica gel flash column chromatography (petroleum ether/ethyl acetate = 9:1) and isolated as an orange-yellow oil (1.135 g, 78%; *E/Z* = 4:1). R_f: 0.35 (petroleum ether/ethyl acetate = 9:1); $[\alpha]_D$: +68.9 (*c* = 0.5 in CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.81 (d, *J* = 7.5 Hz, 1H), 6.84 (d, *J* = 7.0 Hz, 1H), 5.32 (m, 1H), 4.01 (d, *J* = 1 Hz, 2H), 2.55 (dd, *J* = 14.5, 8.5 Hz, 1H), 2.33 (dd, *J* = 14, 7.5 Hz, 1H), 1.53 (s, 3H), 1.27 (s, 3H), 1.00–1.05 ppm (m, 21H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 202.8, 189.3, 168.3, 139.3, 136.0, 115.4, 67.4, 47.9, 34.7, 21.4, 18.0, 17.7, 13.4, 12.0 ppm; IR (film): $\tilde{\nu}$ = 3431, 2940, 2866, 1763, 1719, 1570, 1459, 1382, 1226, 1115, 996 cm^{-1}; HRMS: *m/z* calcd for $C_{17}H_{27}O_3Si$ $[M-i\mathrm{Pr}]^+$: 307.172948; found: 307.172637.



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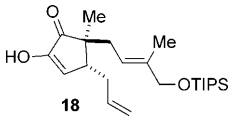
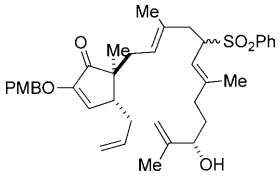
Compound 18: Allyltrimethylsilane (0.14 mL, 0.91 mmol) was added to a suspension of **27** (32 mg, 0.091 mmol) and $MgBr_2\cdot Et_2O$ (70.8 mg, 0.274 mmol) in CH_2Cl_2 at −78 °C. The resulting suspension was stirred at −78 °C for 10 min before it was warmed to 0 °C. Next, the suspension was stirred at 0 °C for 10 min and then it was slowly warmed to room temperature. The mixture was then stirred at room temperature for 1 h before it was poured into a precooled $NaHCO_3$ solution. The mixture was extract-



18

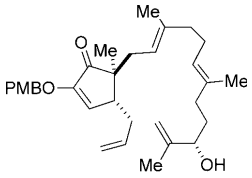
ed with ethyl acetate (10 mL×3) and the combined organic fractions were dried over Na_2SO_4. Compound **18** was purified by silica gel flash column chromatography (petroleum ether/ethyl acetate = 9:1) and isolated as a colorless oil (30.8 mg, 86%, d.r. = 5.7:1). R_f: 0.35 (petroleum ether/ethyl acetate = 9:1); $[\alpha]_D$: −19.6 (c = 1.56 in CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 6.44 (d, J = 3 Hz, 1H), 5.80 (m, 1H), 5.65 (brs, 1H), 5.35 (tt, J = 7.5, 1.5 Hz, 1H), 5.07 (dt, J = 15.5, 1.5 Hz, 2H), 4.04 (s, 3H), 2.61 (ddd, J = 2.5, 5, 10.5 Hz, 1H), 2.37 (td, J = 5.5, 14 Hz, 1H), 2.3–2.2 (m, 2H), 1.92 (m, 1H), 1.80 (s, 3H), 1.05–1.03 ppm (m, 24H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 208.9, 150.7, 137.8, 136.3, 131.4, 117.6, 117.0, 67.8, 48.8, 43.2, 36.1, 35.3, 19.6, 18.1, 13.8, 12.0 ppm; IR (film): $\tilde{\nu}$ = 3355 (br), 2943, 2867, 1694, 1654, 1464, 1394, 1214, 1115, 1066 cm^{-1}; HRMS: m/z calcd for $C_{20}H_{33}O_3Si$ $[M-i\mathrm{Pr}]^+$: 349.219899; found: 349.217262.

Compound 34: LiHMDS (0.62 mL, 0.5 M in THF) was added dropwise to a solution of **16** (65 mg, 0.155 mmol) and **15** (45.7 mg, 0.155 mmol), in THF (0.6 mL) and HMPA (0.2 mL) at −40 °C, under nitrogen. The resulting solution was stirred at −40 °C for 5 min, before it was poured into an ice-cold solution of NaH_2PO_4 (1 M). The mixture was extracted with ethyl acetate (10 mL×3) and the combined organic fractions were dried over Na_2SO_4. The sulfone adducts **34** (mixture of diastereomers) were purified by silica gel flash column chromatography (petroleum ether/ethyl acetate = 7:3, then 1:1) to give a colorless oil (83.7 mg, 85%).



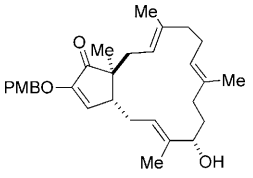
34

Compound 13: DMSO (3 mL) was added to a mixture of the sulfone adducts **34** (242 mg, 0.38 mmol), $[Pd(OAc)_2]$ (17.2 mg, 0.076 mmol) and DPPP (37.6 mg, 0.091 mmol) at room temperature, under N_2. The resulting solution was stirred at room temperature for 15 min before $NaBH_4$ (17.3 mg, 0.46 mmol) was added. The resulting dark mixture was stirred overnight and then it was poured into brine (ca. 25 mL). The mixture was extracted with ethyl acetate (25 mL×3) and the combined organic fractions were dried over Na_2SO_4. Compound **13** was purified by silica gel flash column chromatography (petroleum ether/ethyl acetate = 9:1, then 3:1) to give a colorless oil (163 mg, 77%). R_f: 0.35 (petroleum ether/ethyl acetate = 7:3); $[\alpha]_D$: −11.82 (c = 0.38 in CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.29 (d, J = 8.5 Hz, 2H), 6.87 (d, J = 8.5 Hz, 2H), 6.29 (d, J = 2.5 Hz, 1H), 5.80 (m, 1H), 5.11–5.04 (m, 2H), 5.00 (t, J = 7.5 Hz, 1H), 4.92 (s, 1H), 4.86 (s, 2H), 4.83 (s, 1H), 4.02 (t, J = 6 Hz, 1H), 3.80 (s, 3H), 2.56 (ddd, J = 10, 5, 2.5 Hz, 1H), 2.34 (dt, J = 14, 5.5 Hz, 1H), 2.20–2.18 (m, 2H), 2.06–1.96 (m, 6H), 1.88 (m, 1H), 1.72 (s, 3H), 1.69–1.61 (s, 2H), 1.59 (s, 3H), 1.02 ppm (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 207.2, 159.6, 154.4, 147.5, 138.4, 136.6, 134.9, 130.2, 129.5, 127.9, 124.5, 119.5, 116.9, 113.9, 111.1, 75.7, 71.3, 55.3, 49.5, 43.0, 39.9, 36.6, 35.8, 35.6, 33.2, 26.6, 19.7, 17.7, 16.3, 16.0 ppm; IR (film): $\tilde{\nu}$ = 3480 (br), 3073, 2935, 1715, 1622, 1515, 1455, 1372, 1249, 1034, 913, 824 cm^{-1}; HRMS: m/z calcd for $C_{32}H_{44}O_4$ $[M]^+$: 492.323960; found: 492.322332.



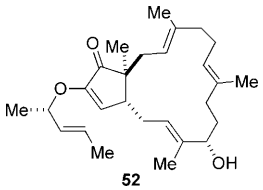
13

Compound 36: Grubbs second-generation catalyst (8.5 mg, 0.01 mmol) was added to a solution of **13** (50.7 mg, 0.10 mmol) in benzene (40 mL) under N_2 at room temperature. The resulting solution was stirred at room temperature for 16 h before it was concentrated in vacuo. Compound **36** was directly purified by silica gel preparative TLC (petroleum ether/ethyl acetate = 1:4, then 2:3) and isolated as a colorless oil (21.1 mg, 44%). R_f: 0.30 (petroleum ether/ethyl acetate = 2:3); $[\alpha]_D$: −42.38 (c = 0.68 in CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.31 (d, J = 8 Hz, 2H), 6.88 (d, J = 7.5 Hz, 2H), 6.24 (d, J = 3.0 Hz, 1H), 5.43 (m, 1H), 5.19 (dd, J = 10, 5 Hz, 1H), 5.08 (m, 1H), 4.90 (dd, J = 24.5, 11.5 Hz, 2H), 4.04 (dd, J = 10, 3 Hz, 1H), 3.80 (s, 3H), 2.75 (dt, J = 10.5, 3 Hz, 1H), 2.40 (dd, J = 13.5, 10.5 Hz, 1H), 2.26–1.96 (m, 8H), 1.80 (m, 3H), 1.62 (d, J = 4.0 Hz, 3H), 1.56 (s, 3H), 0.99 ppm (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 207.8, 159.7, 153.7, 138.0, 136.4, 133.2, 131.7, 129.5, 128.5, 127.9, 124.4, 121.6, 114.0, 76.7, 71.5, 55.4, 49.5, 44.8, 40.2, 38.4, 34.9, 31.0, 30.0, 23.9, 16.9, 15.6, 15.3, 10.5 ppm; IR (film): $\tilde{\nu}$ = 3480 (br), 2934, 1712, 1628, 1516, 1455, 1248, 1156, 1053, 1033 cm^{-1}; HRMS: m/z calcd for $C_{30}H_{40}O_4$ $[M]^+$: 464.292660; found: 464.290731.



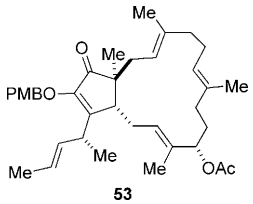
36

Compound 52: In a flame-dried, argon-purged round-bottom flask $[Pd_2(dba)_3]\cdot CHCl_3$ (1.5 mg, 0.0015 mmol) and (*S*,*S*)-L_{ST} (3.0 mg, 0.0044 mmol) were combined and dissolved in dry, deoxygenated CH_2Cl_2 (0.5 mL). Compound **42**[35] (23.2 mg, 0.118 mmol) was then added to this solution. The resulting yellow solution was stirred at room temperature for 15 min, at which time a solution of **37** (20.3 mg, 0.059 mmol) in dry, deoxygenated CH_2Cl_2 (0.7 mL) was added slowly over 1 h by syringe pump. After this addition, the solution was concentrated in vacuo and compound **52** was purified by silica gel flash column chromatography (petroleum ether/ethyl acetate = 4:1, then 7:3) to give a colorless oil (19.2 mg, 89%, d.r. > 15:1). R_f: 0.35 (petroleum ether/ethyl acetate = 4:1); $[\alpha]_D$: −57.33 (c = 0.85 in CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 6.18 (d, J = 3H, 1H), 5.67 (m, 1H), 5.47 (m, 1H), 5.42 (dd, J = 6, 4.5 Hz, 1H), 5.20 (dd, J = 10, 5.5 Hz, 1H), 5.10 (dd, J = 7.5, 5 Hz, 1H), 4.57 (m, 1H), 4.04 (m, 1H), 2.74 (dt, J = 11, 3 Hz, 1H), 2.39 (dd, J = 14, 10.5 Hz, 1H), 2.26–1.95 (m, 7H), 1.82–1.76 (m, 3H), 1.71 (dd, J = 6.5, 1.5 Hz, 3H), 1.63 (s, 3H), 1.62 (s, 3H), 1.55 (s, 3H), 1.39 (s, 3H), 0.97 ppm (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 208.5, 152.6, 137.9, 136.3, 133.1, 132.5, 131.2, 128.7, 128.4, 124.4, 121.7, 76.70, 76.67, 49.2, 44.9, 40.3, 38.5, 34.9, 31.1, 29.9, 23.9, 21.1, 17.7, 16.8, 15.6, 15.4, 10.5 ppm; IR (film): $\tilde{\nu}$ = 3448 (br), 2934, 1708, 1625, 1438, 1376, 1309, 1245, 1157, 1050 cm^{-1}; HRMS: m/z calcd. for $C_{27}H_{40}O_3$ $[M]^+$: 412.297746; found: 412.297427.



52

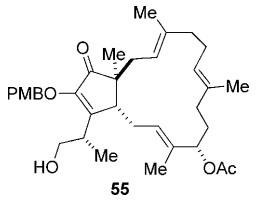
Compound 53: Compound **52** (9.1 mg, 0.022 mol) was dissolved with DME (2.5 mL) in a microwave vial under N_2. The solution was heated at 150 °C under microwave irradiation for 1 h, before the solvent was removed under vacuum. $CsCO_3$ (14.3 mg, 0.044 mmol), Bu_4NI (1.6 mg, 0.0044 mmol) and DMF (0.22 mL) were added to the residue at room temperature, under N_2. The resulting mixture was stirred at room temperature for 15 min, before PMBCl (5.2 mg, 0.033 mmol) was added. The resulting suspension was then stirred in the dark for 2 h before it was poured into brine. The mixture was then extracted with ethyl acetate (10 mL×3) and the combined organic fractions were dried over Na_2SO_4. After it was purified by silica gel flash column chromatography (10% v/v diethyl ether in petroleum ether, then 25% v/v ethyl acetate in petroleum ether), this PMB ether (≈11.6 mg) was dissolved with pyridine (0.1 mL) and acetic anhydride (0.1 mL) at 0 °C. The resulting solution was stirred at room temperature for 3 h, before it was concentrated under vacuum. Compound **53** was then purified by silica gel flash column chromatography (petroleum ether/diethyl ether = 9:1, then petroleum ether/ethyl acetate = 9:1) to give a light-yellow oil (8.7 mg, 69%, over three steps). R_f: 0.35 (petroleum ether/ethyl acetate = 9:1); $[\alpha]_D$: −89.58 (c = 0.26 in CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.29 (d, J = 8.5 Hz, 2H), 6.86 (d, J = 8.5 Hz, 2H), 5.43–5.32 (m, 3H), 5.25–5.11 (m, 5H), 3.80 (s, 3H), 3.15 (m, 1H), 2.60 (dd, J = 11, 3 Hz, 1H), 2.36 (d,



53

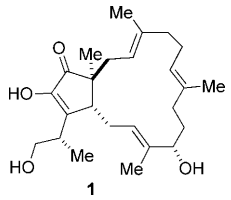
$J=17$ Hz, 1H), 2.30–2.20 (m, 3H), 2.14–2.00 (m, 6H), 1.85–1.79 (m, 3H), 1.72–1.67 (m, 2H), 1.64 (s, 3H), 1.61 (s, 3H), 1.59 (d, $J=5.5$ Hz, 3H), 1.53 (s, 3H), 1.16 (d, $J=7$ Hz, 3H), 0.94 ppm (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): $\delta=209.1$, 170.4, 162.4, 159.5, 148.4, 137.7, 132.6, 132.4, 131.9, 131.6, 130.5, 129.6, 124.9, 124.3, 121.8, 113.7, 78.8, 71.1, 55.3, 49.7, 47.1, 40.2, 39.3, 37.1, 34.6, 29.5, 27.7, 23.9, 21.6, 17.88, 17.87, 16.2, 15.7, 15.5, 11.1 ppm; IR (film): $\tilde{\nu}=2920$, 2851, 1732, 1698, 1634, 1613, 1514, 1463, 1370, 1247, 1019 cm^{-1}; HRMS: m/z calcd for $C_{37}H_{50}O_5$ $[M]^+$: 574.365825; found: 574.367201.

Compound 55: A solution of **53** (6.5 mg, 0.011 mmol) in *t*BuOH (0.05 mL) was added to a mixture of AD-α-mix (21.1 mg) and $CH_3SO_2NH_2$ (1.6 mg, 0.017 mmol) in H_2O (0.1 mL) and *t*BuOH (0.05 mL) at 0 °C. The resulting mixture was stirred at 4 °C for 2 days, before it was quenched with Na_2SO_3 and brine. The mixture was extracted with ethyl acetate (10 mL × 3) and the combined organic fractions were dried over Na_2SO_4. Diols **54** (mixture of diastereomers) were purified by silica gel flash column chromatography (petroleum ether/ethyl acetate = 7:3, then 1:1) to give a colorless oil (4.5 mg, 65%; 1.2 mg of **53** was recovered). $NaIO_4$ (19 mg, 0.089 mmol) was added to a solution of diol **54** (9.0 mg, 0.015 mmol) in THF/H_2O (4:1, 0.2 mL), at 0 °C. The resulting solution was stirred at room temperature for 1 h, before it was quenched with brine. The mixture was then extracted with ethyl acetate (10 mL × 3) and the combined organic fractions were dried over Na_2SO_4. After the solvent was removed in vacuo, the crude aldehyde was dissolved with a mixture of CH_2Cl_2 (0.1 mL) and MeOH (0.1 mL). The resulting solution was cooled to −78 °C before $NaBH_4$ (3 mg, 0.065 mmol) was added. The mixture was stirred at −78 °C for 0.5 h before it was quenched with a mixture of acetone (0.05 mL) and brine (3 mL). The resulting mixture was extracted with ethyl acetate (3 mL × 3) and the combined organic fractions were dried over Na_2SO_4. Compound **55** was purified by silica gel flash column chromatography (petroleum ether/ethyl acetate = 7:3, then 3:2) to give a colorless oil (6.5 mg, 78%). R_f: 0.35 (petroleum ether/ethyl acetate = 7:3); $[\alpha]_D$: −57.36 ($c=0.60$ in CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta=7.29$ (d, $J=8$ Hz, 2H), 6.87 (d, $J=8$ Hz, 2H), 5.44 (m, 1H), 5.35 (d, $J=11$ Hz, 1H), 5.21 (dd, $J=10$, 6 Hz, 1H), 5.12 (d, $J=11.5$ Hz, 1H), 5.10 (m, 1H), 3.80 (s, 3H), 3.62 (m, 2H), 2.64–2.60 (m, 2H), 2.34–2.22 (m, 5H), 2.13–2.00 (m, 4H), 2.00 (s, 3H), 1.92–1.65 (m, 4H), 1.63 (s, 3H), 1.54 (s, 3H), 1.43 (s, 3H), 1.11 (d, $J=7$ Hz, 3H), 0.96 ppm (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): $\delta=208.9$, 170.5, 160.9, 159.7, 149.2, 138.0, 132.4, 131.9, 131.7, 130.6, 129.2, 124.5, 121.6, 113.8, 79.0, 66.1, 55.4, 49.8, 49.0, 40.2, 39.4, 37.7, 34.6, 28.9, 27.5, 23.9, 21.6, 16.5, 15.6, 15.5, 14.6, 11.1 ppm; IR (film): $\tilde{\nu}=3462$ (br), 2923, 2851, 1734, 1700, 1637, 1612, 1515, 1248, 1035, 1019 cm^{-1}; HRMS: m/z calcd for $C_{25}H_{36}O_3$ $[M-\text{PMB}-\text{OAc}]^+$: 384.266445; found: 384.262829.



55

Compound 1 (terpestacin): LiOH (0.06 mL, 1 M) was added to a solution of **55** (7.3 mg, 0.013 mmol) in THF (0.18 mL) and MeOH (0.06 mL) at room temperature. The resulting solution was stirred at room temperature for 2 h, before it was quenched with NaH_2PO_4 (1 M). The mixture was extracted with ethyl acetate (10 mL × 3) and the combined organic fractions were dried over Na_2SO_4. The diol was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 1:1, then 3:7) to give a colorless oil (6.0 mg, 89%). Dry DMS (0.015 mL) was added to a mixture of the above diol (3.0 mg, 0.0057 mmol) and $MgBr_2{\cdot}Et_2O$ (14.5 mg, 0.056 mmol) in CH_2Cl_2 (0.2 mL) at −78 °C. The resulting suspension was stirred at −78 °C for 10 min, before it was warmed to 0 °C. The suspension was stirred at 0 °C for 10 min and then slowly warmed to room temperature. The mixture was stirred at room temperature for 40 min, before it was poured into a precooled NaCl solution (10 mL). The mixture was extracted with ethyl acetate (10 mL × 3) and the combined organic fractions were dried over Na_2SO_4. Preparative silica gel TLC (10% MeOH in CH_2Cl_2) afforded (−)-terpestacin **1** (1.7 mg, 74%). R_f: 0.3 (10% MeOH in CH_2Cl_2); $[\alpha]_D$: −17.7 ($c=0.085$ in MeOH); ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta=5.89$ (brs, 1H), 5.40 (m, 1H), 5.24 (dd, $J=10$, 5.0 Hz, 1H), 5.13 (m, 1H), 4.06 (dd, $J=10$, 3.5 Hz, 1H), 3.89 (dd, $J=10.5$, 7.0 Hz, 1H), 3.82 (dd, $J=10$, 5.5 Hz, 1H), 2.71 (dd, $J=11.5$, 2.0 Hz, 1H), 2.68 (m, 1H), 2.44 (d, $J=17.0$ Hz, 1H), 2.39 (dd, $J=13.5$, 10.5 Hz, 1H), 2.29–2.21 (m, 2H), 2.13–2.08 (m, 2H), 2.04–1.89 (m, 2H), 1.79–1.67 (m, 3H), 1.64 (s, 3H), 1.63 (s, 3H), 1.57 (s, 3H), 1.29 (d, $J=7.0$ Hz, 3H), 1.00 ppm (s, 3H); IR (film): $\tilde{\nu}=3347$ (br), 2923, 2853, 1694, 1645, 1455, 1029 cm^{-1}; HRMS: m/z calcd for $C_{25}H_{38}O_4$ $[M]^+$: 402.277010; found: 402.275848.



1

Acknowledgements

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