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Total Synthesis of (±)-Terpestacin and (±)-11-*epi*-Terpestacin

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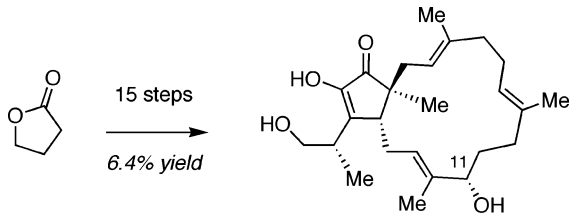

(±)-1 *terpestacin*

The total synthesis of racemic terpestacin and 11-*epi*-terpestacin using the allene ether Nazarov reaction as the key step is described. All stereochemistry is derived from the stereogenic carbon atom that is formed during the Nazarov reaction.

Introduction

Terpestacin (**1**) is a sesterterpene natural product that is produced by a number of fungi. It was first isolated in 1993 by Oka and co-workers from an *Arthrinium* species.[1] In 2001 Gräfe and co-workers isolated terpestacin from a *Ulocladium* fungus; however, they assigned the enantiomeric structure to their isolate.[2] In 2002 Miyagawa and co-workers reported the isolation of siccanol, to which they assigned the 11-*epi*-terpestacin structure, from yet a third fungal source, *Bipolaris sorokiniana*.[3] As was subsequently demonstrated by Jamison's total synthesis of (−)-terpestacin and 11-*epi*-terpestacin, siccanol is identical to terpestacin.[4] The C24 acetoxy derivative of terpestacin, fusaproliferin, was isolated by Randazzo and co-workers in 1993 from *Fusarium proliferatum*, a fungal pathogen of maize.[5] In the case of fusaproliferin there was some initial confusion regarding the assignment of absolute configuration. Myers' total synthesis of (−)-terpestacin and (−)-fusaproliferin defined the correct absolute configuration as well as the specific rotations for both natural products.[6] Myers suggested that errors in the optical rotations that had been reported for these natural products, both during the isolation and early synthesis work, could be traced to an unusual and unrecognized intramolecular chloroetherification reaction that took place in chloroform, the solvent that was used for the optical rotation measurements. A very clear and informative description of the chronology of all the discovery and synthesis work associated with terpestacin and fusaproliferin through the middle of 2004 can be found in Jamison's paper.[4a]

Terpestacin is a potent inhibitor (ID_{50} 0.46 μg/mL) of the formation of syncytia, large multinucleated cells that are associated with the pathology of HIV infection.[1c,2] It has also been reported to inhibit angiogenesis on the basis of assays in bovine aortic endothelial cells and in chorioallantoic membrane from chick embryos.[7] Furthermore, terpestacin has been reported to have only modest antimicrobial activity, suggesting that it is not an indiscriminate cytotoxin and may therefore be a useful lead compound for the development of anticancer as well as anti-AIDS chemotherapeutics.

As a consequence of the novelty of the structure as well as the promising activity, work on the total synthesis of terpestacin

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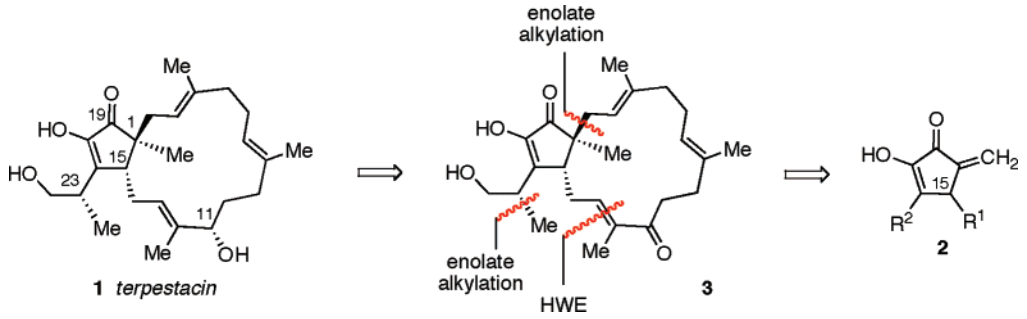

FIGURE 1. Retrosynthesis of terpestacin.

was initiated soon after its discovery. To date four syntheses of (−)-terpestacin have been reported, by Tatsuta (1998),[8] Myers (2002),[6] Jamison (2003),[4a] and most recently by Trost (2007).[9] In 1998 Tatsuta also reported a synthesis of the racemate.[8] Approaches to the terpestacin ring system were described by Takeda (1995)[10] and by Heissler (1999).[11] In 2005 we disclosed a synthesis of the cyclopentenone core structure of terpestacin.[12] In what follows we describe our concise total synthesis of the racemate of **1** that makes use of a unique strategy for stereochemical control at C23 and C11, and that employs the allene ether version of the Nazarov reaction in the key step (Figure 1). All stereochemistry is derived from the stereogenic carbon atom that is formed during the Nazarov reaction.

Results and Discussion

The core α-hydroxycyclopentenone structure of terpestacin closely matches structure **2** that is easily prepared by means of the allene ether Nazarov reaction.[13] This suggested a very direct strategy for the total synthesis, in which the C15 (terpestacin numbering) stereocenter that is formed during the Nazarov cyclization is used to direct stereochemistry at C1 and at C23. The macrocyclic portion of the molecule would be assembled by means of an intramolecular Horner−Wadsworth−Emmons (HWE) reaction. We intended to prepare the racemate of **1** before proceeding to an enantioselective synthesis.[14] A potential difficulty associated with the synthesis of the racemate relates to C11. Whereas stereochemical control at C11 in the homochiral series might be exercised through asymmetric reduction of a C11 ketone (as in **3**), in the racemic series we would have to rely on substrate control alone.[15] Chemoselectivity in favor of C11 reduction seemed plausible, since reduction at C18 is certain to be impeded by the presence of the adjacent quaternary carbon atom. We had speculated that stereoselective reduction at C11 in **3** might also be possible by relying on whatever steric bias the macrocycle had introduced to the diastereotopic faces of the carbonyl group. Unfortunately, upon examining a molecular model, the macrocycle appeared to have many degrees of freedom, making it impossible to predict a direction for sterically favored approach of hydride. Nor was examination of the crystal structure of terpestacin illuminating in this regard.[6,1c] Tatsuta had, however, reported modest selectivity for reduction of a C11 macrocyclic ketone intermediate in his synthesis of racemic terpestacin.[8] Also, a bias for reduction to the undesired β-C11 diastereomer would not doom the synthesis to failure, since Mitsunobu inversion would presumably give access to the natural product.[16]

Our model study had demonstrated that relaying stereochemical information from C15 to C1 and then to C23 was a successful strategy.[12] Condensation of 1-lithio-1-(methoxy)-methoxyallene **5**[17] with lactone **4**, derived in two steps from γ-butyrolactone, led to cyclopentenone **6** in 65% yield (Scheme 1). Protection of the diol function by exposure of **6** to 2-methoxypropene and catalytic acid led to acetonide **7** in 91% yield. Selective saturation of the exocyclic double bond in **7** gave **8** as a single diastereomer in quantitative yield. The enolate derived from **8** was trapped with allylic bromide **16** (Scheme 2), leading to **9** as a single isomer in 75% yield.

The synthesis of **16** (Scheme 2) starts from known epoxide **14** that is derived from the corresponding bromohydrin by exposure to DBU.[18] Oxidative cleavage of the epoxide with periodic acid[19] was followed by sequential treatment with acidic methanol and K_2CO_3 to give allylic alcohol **15** in 79% yield from **14**. Conversion of **15** to the labile bromide **16** took place by displacing the derived mesylate with LiBr (80% yield). An alternative electrophile for alkylation at C1 was required (*vide infra*); therefore, allylic bromide **20** was also prepared from **14**.[8] Aldehyde **17** was derived from oxidative cleavage of **14** in 85% yield. Exposure of **17** to lithium ethyldiethylphosphonate resulted in nucleophilic addition to the aldehyde carbonyl group with simultaneous cleavage of the acetate. Acetylation of the primary allylic alcohol in a second step led to **18** that was immediately converted to the corresponding *tert*-butyldimethylsilyl ether. Methanolysis of the acetate group gave **19** in 68% overall yield for the four steps from **17**. Sequential exposure of **19** to MsCl and LiBr led to allylic bromide **20** in 90% yield.

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(14) (a) delos Santos, D.; Banaag, A. R.; Tius, M. A. *Org. Lett.* **2006**, *8*, 2579−2582. (b) Harrington, P. E.; Murai, T.; Chu, C.; Tius, M. A. *J. Am. Chem Soc.* **2002**, *124*, 10091−10100.
(15) For an exquisite example of substrate control of stereochemistry in the synthesis of the racemate of a natural product, see: Wang, Y.; Janjic, J.; Kozmin, S. A. *J. Am. Chem. Soc.* **2002**, *124*, 13670−13671.
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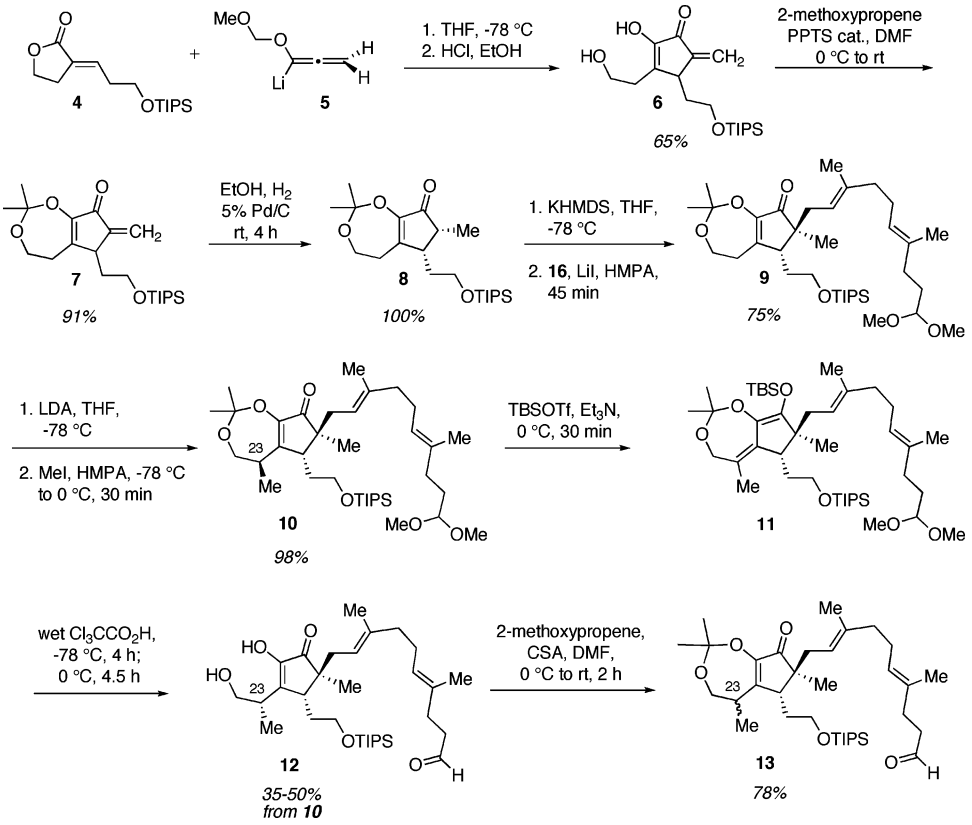
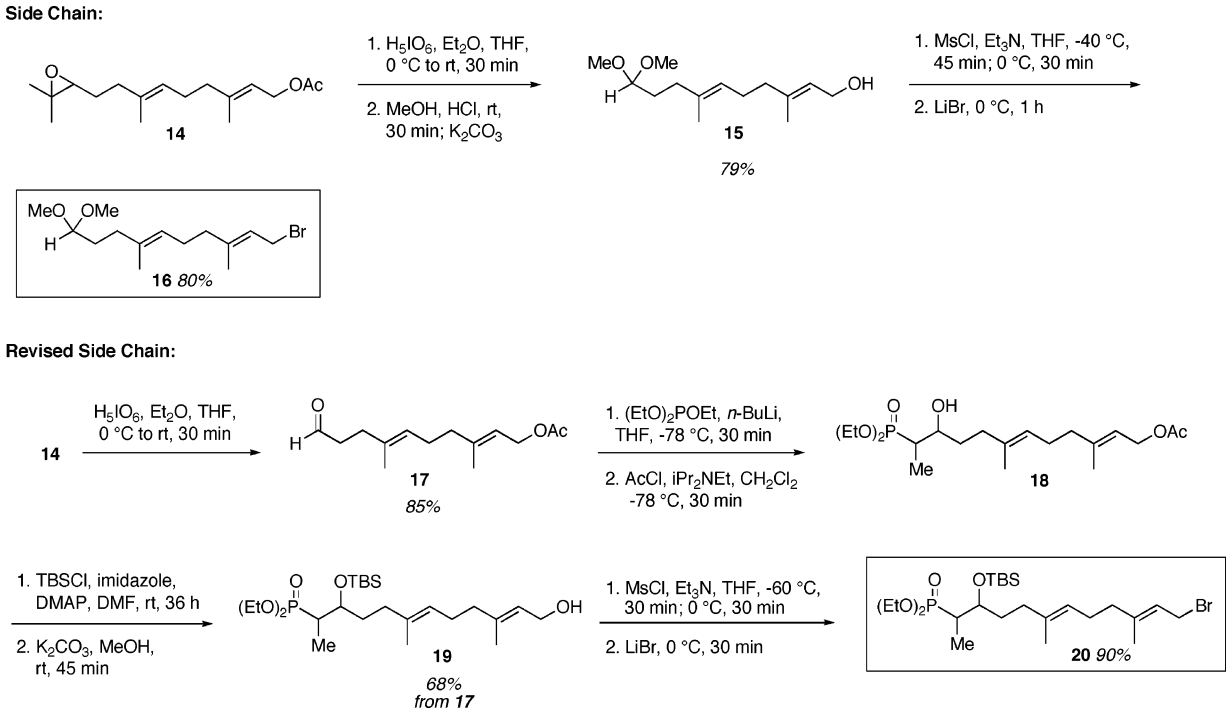
(19) Marshall, J. A.; Mikowski, A. M. *Org. Lett.* **2006**, *8*, 4375−4378.

SCHEME 1. Preparation of Aldehyde 13



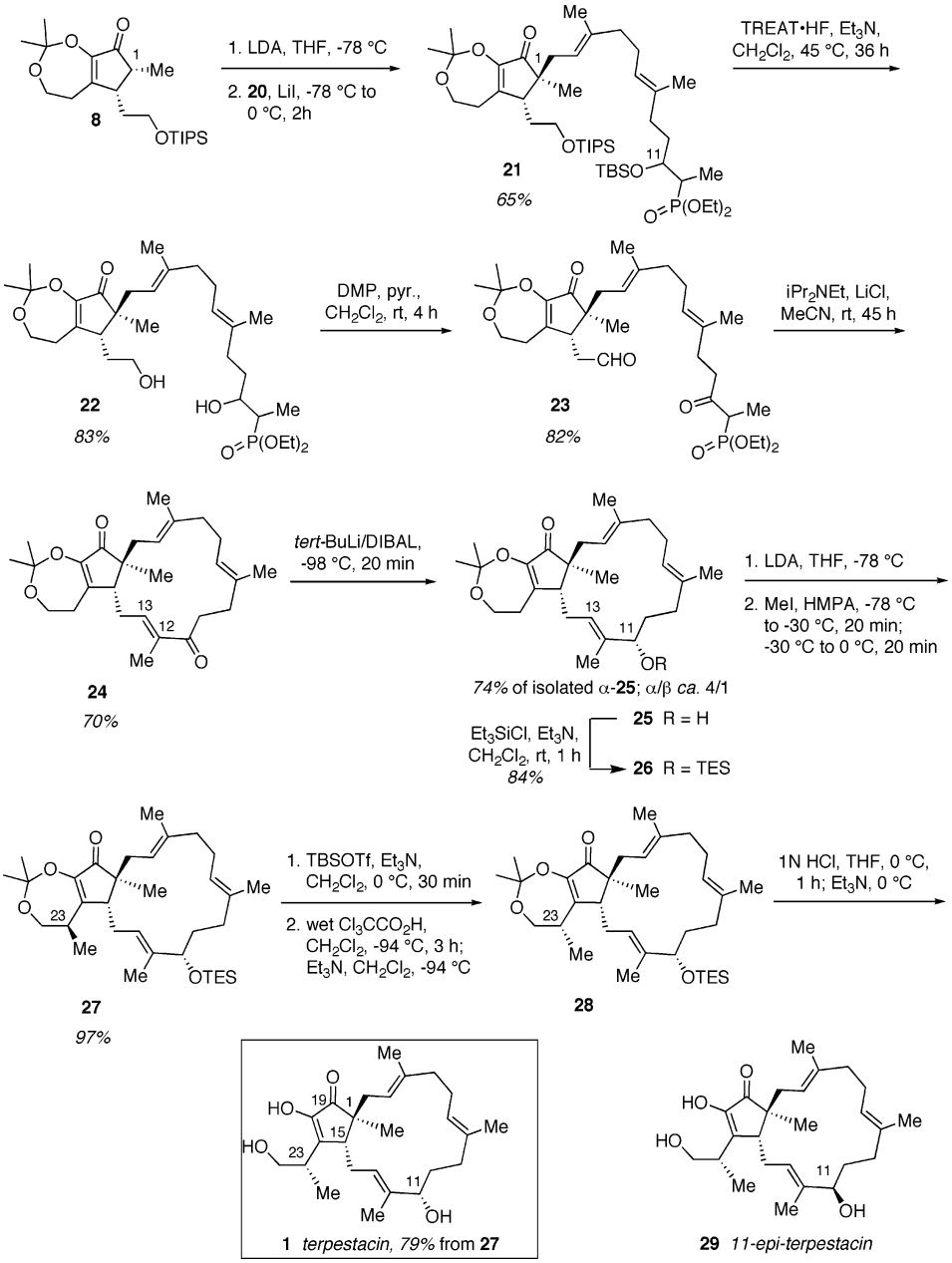
SCHEME 2. Preparation of Electrophiles 16 and 20



Returning to the core synthesis, the extended enolate derived from **9** (Scheme 1) was formed by exposure to LDA and was trapped at C23 with iodomethane to produce **10** in 98% isolated yield. The stereochemistry at C23 is assumed to be β as shown in **10** on the basis of our earlier work[12] and results from approach of the electrophile cis to the C15 hydrogen atom. The C23 stereochemistry in **10** was inverted by exploiting the same stereochemical bias that led to its formation. Exposure of **10** to *tert*-butyldimethylsilyl triflate and triethylamine[20] led to extended enol ether **11** that was protonated at −78 °C with wet trichloroacetic acid. Proton approach from the least hindered

(20) The use of Hünig's base in this reaction fails to produce the silyl enol ether.

SCHEME 3. The Synthesis of (±)-Terpestacin



face of the dienol ether leads to the desired α-C23 stereochemistry. Higher temperature and longer exposure to acid was required in order to hydrolyze the dimethyl acetal group. Under these conditions loss of the acetonide also took place, leading to **12** in 35−50% yield, along with several unidentified byproducts. The diol was reprotected as the acetonide to give **13** in 78% yield. The obvious problem of this approach is the low yield for the conversion of **10** to **12**. Another problem was detected in the 500 MHz ^{1}H NMR spectrum of **13** which revealed the presence of two aldehyde protons in the approximate ratio of 2/1. The minor aldehyde peak may represent the C23 diastereomer of **13**. Since **10** appeared to be incompatible with the acidic conditions that are necessary for hydrolysis of the dimethyl acetal, and since epimerization at C23 was likely to be a recurring problem, the approach of Scheme 1 was modified.

The revised synthesis that led to (±)-terpestacin is outlined in Scheme 3. A more convergent approach is possible by introducing the phosphonate function needed for the macrocyclization during the alkylation of **8.**[21] This meant that the introduction and subsequent inversion of the C23 methyl group could not be conducted immediately following the alkylation of **8,** as we had successfully done in the model study. Instead, we risked deferring this difficult stereochemical problem until the very end of the synthesis. Trapping the lithio enolate of **8** with allylic bromide **20** (Scheme 2) led to **21** in 65% yield as a single isomer.[22] Starting material **8** was not recovered from the alkylation; therefore, proton transfer from **20** or **21** to the

(21) This approach was utilized by Tatsuta on a much different substrate. See refs 8a and 8b.

(22) The 300 MHz ^{1}H NMR spectrum of **21** does not show evidence of the C1 diastereomer. However, the presence of diastereomers at C11 and C12 of **21** precluded the use of ^{13}C NMR for the detection of C1 diastereomers. In the event, compound **24** was isolated as a *single* (^{1}H and ^{13}C NMR) diastereomer, suggesting that if the alkylation of **8** had led to a C1 diastereomeric mixture, the proportion of the minor isomer was very small.

enolate of **8** cannot account for the modest yield. Simultaneous cleavage of the TBS and TIPS protecting groups in **21** took place with $Et_3N{\cdot}3HF$ (TREAT·HF) in the presence of added triethylamine to produce diol **22** in 83% yield with no loss of the acetonide.[23] The use of TBAF in this reaction led to extensive decomposition of product, and buffering the highly basic TBAF did not lead to any silyl ether cleavage. Simultaneous oxidation of primary and secondary hydroxyl groups in **22** with the Dess−Martin periodinane led to ketophosphonate **23** in 84% yield. The subsequent macrocyclization proved to be sensitive to the conditions for the intramolecular HWE reaction. Exposure of **23** to triethylamine and LiCl in acetonitrile led to **24** in *ca.* 50% yield, along with an unidentified byproduct. Varying the concentration of the reaction from 0.01 to 0.005 M did not affect the outcome, but switching from triethylamine to Hünig's base solved the problem and led to **24** in 70% yield after 45 h at rt.[24] The *E* geometry of the C12−C13 double bond was confirmed by NOE.[25]

The critical reduction of the C11 ketone was first attempted using DIBAL in toluene at −78 °C, conditions that were suggested by Tatsuta's work.[8] In the case of **24** it soon became apparent that under these conditions little or no stereoselectivity would be observed. Furthermore, as the reaction progressed, reduction at C18 was observed, along with unreacted **24**, indicating that the reaction was neither sufficiently chemoselective nor stereoselective. The reactivity of DIBAL in ethereal solvents is attenuated relative to hydrocarbons, so when the reduction of **24** was conducted in THF at −78 °C the reaction was slower, but stereo- and chemoselectivity did not change. Neither was product distribution substantially affected when the reduction was performed at −98 °C.

Since DIBAL presumably engages the nonbonding electron pair of the carbonyl oxygen atom prior to transferring hydride intramolecularly, the insensitivity of the reaction to variations in temperature and even solvent is understandable. We hoped that by using an aluminate rather than an alane we could alter the mechanism of the reduction so as to exercise control on the stereoselectivity, and perhaps also on the chemoselectivity. This hypothesis was borne out. Exposure of **24** to *n*-BuLi/DIBAL in toluene at −78 °C for 30 min led to a *ca.* 2/1/1 mixture of α-C11 and *β*-C11 alcohols and unreacted **24**. A trace of the over-reduced C11−C18 diol was also formed. Switching to *tert*-BuLi/DIBAL in THF at −98 °C led to **25** and its *β*-C11 diastereomer in 74% and 20% isolated yield, respectively.[26] There was no unreacted starting material and no over-reduced product observed in this reaction. The use of the aluminate reagent provided a satisfying solution to the problem of C11 stereochemistry, particularly since the two diastereomeric alcohols were easily separable by chromatography. The minor *β*-C11 alcohol was independently converted to 11-*epi*-terpestacin **29**.

Introduction of the C23 methyl group with the proper stereochemistry remained the final obstacle. The C11 hydroxyl was protected as the TES ether (84% yield) in preparation for the enolate alkylation. Deprotonation of **26** with LDA followed by exposure of the enolate to iodomethane in the presence of HMPA led to **27** in 97% yield as a single isomer. The alkylation is somewhat sluggish and seems to take place as the solution is warmed from −30 °C to 0 °C.[27] Adjustment of stereochemistry at C23 was accomplished as in the model study. Enone **27** was converted to the TBS dienol ether that was treated with wet trichloroacetic acid in dichloromethane at −94 °C for 3 h. The reaction was quenched at −94 °C by addition of excess triethylamine to give the desired α-C23 methyl diastereomer **28**. The *β*-C23 diastereomer was barely detectable (<5%) in the ^{1}H NMR spectrum of the crude reaction mixture.[28] Simultaneous removal of acetonide and silyl ether protecting groups by exposure to 1 N HCl in THF at 0 °C led to (±)-terpestacin in 79% overall yield from **27** following column chromatography on silica gel.

Since the TBS dienol ether hydrolysis as well as the removal of protecting groups required acid, we had tried to combine all operations in a single step. Although the enol ether hydrolysis had proceeded cleanly, during the time that the reaction mixture was allowed to warm to 0 °C, as required for cleavage of the protecting groups, several byproducts appeared. This observation may be related to the sensitivity of terpestacin to acid in dichloromethane solution noted by Oka (eq 1).[1c] For example, exposure of terpestacin to toluenesulfonic acid in dichloromethane overnight led to rearranged product **30** in 61% yield (Figure 2). The mechanism for the formation of **30** presumably involves acid-mediated loss of water from **1** to give a C11−C13 diene as an intermediate. Reprotonation at C11 and intramolecular trapping of the resulting allylic carbocation leads to **30**.

Summary and Conclusions

In summary, a 15 step synthesis of (±)-terpestacin in 6.4% overall yield from *γ*-butyrolactone has been described. There

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(25) A positive NOE (gradient) was observed for the C11 methine and C13 vinyl protons of **26**.

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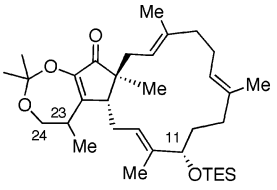
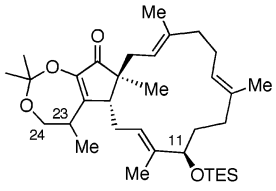
(27) The chromatographic separation of **27** from **26** is very difficult; therefore, pains must be taken to ensure that the reaction proceeds to completion. The iodomethane was distilled and filtered through basic alumina prior to use. The HMPA must be freshly distilled.

(28) C23 diastereomers **27** and **28** are not separable by TLC but can be distinguished easily by ^{1}H NMR at 300 MHz ($CDCl_3$). The signal for the C23 *β* methyl in **27** is observed at 0.78 ppm, whereas the α C23 methyl in **28** is at 1.15 ppm. The C24 methylene protons in **27** appear at 3.68 and 3.58 ppm (both are dd), whereas in **28** they appear at 3.58 and 3.33 (both dd). The same trend in chemical shifts is observed in the C11-epi series of C23 diastereomers.



C23 β-Me (**27**) δ 0.78 (C23-CH_3), 3.68, 3.58 (C24-CH_2)
C23 α-Me (**28**) δ 1.15 (C23-CH_3), 3.58, 3.33 (C24-CH_2)



C23 β-Me δ 0.77 (C23-CH_3), 3.72-3.59 (C24-CH_2)
C23 α-Me δ 1.13 (C23-CH_3), 3.59, 3.35 (C24-CH_2)

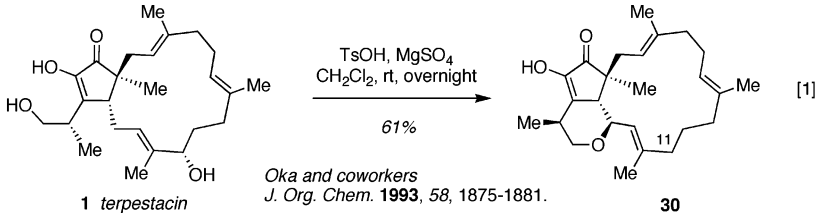


FIGURE 2. Acid-catalyzed rearrangement of terpestacin.

are several features that contribute to the brevity of this total synthesis. The allene ether Nazarov cyclization forms the central α-hydroxycyclopentenone core very early in the sequence and generates the C15 stereocenter that was used to control all others. Substrate-controlled reduction of macrocyclic ketone **24** took place chemo- and stereoselectively. The stereochemistry of methylation at C23 in **26** under control of the C15 stereocenter that leads to the β-methyl group is inverted by protonating the derived silyl dienol ether, again under the directing influence of C15. Since all stereochemistry is derived from the single stereogenic carbon atom that is formed during the Nazarov reaction, an enantioselective terpestacin synthesis by means of an asymmetric Nazarov reaction offers an appealing strategy that we hope to explore.

Experimental Section

(2*E*,6*E*)-11-(Diethoxyphosphoryl)-10-hydroxy-3,7-dimethyldodeca-2,6-dienyl Acetate 18. To a solution of diethyl ethylphosphonate (4.9 mL, 5.04 g, 30.3 mmol) in 0.6 L of THF at −78 °C was added **17** (2.64 g, 11.4 mmol) over 4 Å molecular sieves in 120 mL of THF rapidly by cannula. The solution was maintained at −78 °C and stirred vigorously.[29] The reaction was monitored by TLC and quenched after 30 min by rapid addition by cannula of glacial HOAc (2.4 g, 40.0 mmol) in 50 mL of MeOH that had been cooled to −78 °C. The reaction was warmed to rt, diluted with Et_2O, and washed 3× with satd $NaHCO_3$. The combined aqueous layers were back extracted 3× with Et_2O. The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated. The crude product was partially purified by flash chromatography on silica gel (0.5% to 10% MeOH in CH_2Cl_2) to provide the diol (**S1**; see the Supporting Information) as a mixture of diastereomers (approximately 90% pure) that was suitable for use in the subsequent reaction.[30] Diol: $R_f = 0.23$ (7% MeOH in CH_2Cl_2); ^{1}H NMR (500 MHz, C_6D_6) δ 5.63−5.54 (m, 1H), 5.33 (t, $J = 7.0$ Hz, 0.33H), 5.29 (t, $J = 6.5$ Hz, 0.66H), 4.56 (s, 0.33H), 4.30−4.10 (m, 3.33H), 4.10−3.75 (m, 5.33H), 2.44−1.78 (m, 8.33H), 1.70−1.40 (m including singlets at 1.62, 1.56 and 1.53, 6.66H), 1.23 (dd, $J = 18.5$, 7.5 Hz, 0.66H), 1.16 (dd, $J = 18.5$, 7.5 Hz, 0.33H), 1.10−0.94 (m, 6H); IR (neat) 3393 (br), 2980, 2930, 1445, 1390, 1212 cm^{-1}; EIMS *m*/*z* 362 (M$^+$, 1), 344 (2); HREIMS calcd for $C_{18}H_{35}O_5P$ 362.2222, found 362.2231. To the crude diol and diisopropylethylamine (4.2 mL, 3.15 g, 24.4 mmol) in 60 mL of CH_2Cl_2 at −78 °C was added acetyl chloride (750 μL, 0.84 g, 10.7 mmol). The reaction was monitored carefully by TLC, and additional acetyl chloride was added in small portions (50−150 μL) to ensure complete acylation only of the primary alcohol. The reaction was quenched with the addition of 1 mL of MeOH, diluted with CH_2Cl_2, and extracted 3× with pH 7 buffer. The aqueous layers were back extracted 3×, and the combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated to provide crude **18** as a mixture of diastereomers that was taken on to the next step.

Diethyl (6*E*,10*E*)-3-(*tert*-Butyldimethylsilyloxy)-12-hydroxy-6,10-dimethyldodeca-6,10 -dien-2-ylphosphonate 19. To a solution of crude **18**, imidazole (5.70 g, 84.0 mmol), and DMAP (150 mg, 1.23 mmol) in 40 mL of DMF was added TBSCl (9.2 g, 61.0 mmol) at rt. After 36 h, the reaction was diluted with Et_2O and washed 3× with pH 7 buffer. The aqueous phase was back extracted 3×, and the combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated to provide the crude acetoxy silyl ether[31] as a mixture of diastereomers. The crude product was dissolved in 60 mL of MeOH and treated with K_2CO_3 (1.68 g, 12.2 mmol) at rt. The reaction was monitored by TLC and after 45 min was diluted with Et_2O and extracted 3× with pH 7 buffer. The combined aqueous extract was back extracted 3×, and the combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated. The crude product was purified by flash chromatography on silica gel (10 to 80% EtOAc in hexanes) to provide **19** (3.70 g, 68% overall yield from **17**) as a greenish oil and as a mixture of diastereomers: $R_f = 0.30$ (50% EtOAc in hexanes); ^{1}H NMR (500 MHz, C_6D_6) δ 5.63 (t, $J = 5.5$ Hz, 1H), 5.39 (t, $J = 7.0$ Hz, 0.33H), 5.36 (t, $J = 6.5$ Hz, 0.66H), 4.34−4.24 (m, 2.33H), 4.18−4.10 (m, 0.66H), 4.02−3.84 (m, 4H), 3.50 (br s, 0.33H), 3.36 (br s, 0.66H), 2.38−1.98 (m, 9H), 1.92−1.80 (m, 1H), 1.67 (s, 1H), 1.64 (s, 2H), 1.53 (s, 3H), 1.33 (dd, $J = 18.5$, 7.5 Hz, 1H), 1.25 (dd, $J = 18.0$, 7.5 Hz, 2H), 1.08−1.00 (m including singlet at 1.01, 12H), 0.97 (s, 3H), 0.16 (s, 2H), 0.13 (s, 3H), 0.09 (s, 1H); IR (neat) 3410 (br), 2930, 1668, 1461, 1339, 1251 cm^{-1}; EIMS *m*/*z* 419 (M$^+$ − *t*Bu, 30), 403 (52), 401 (100), 326 (8); HREIMS calcd for $C_{20}H_{40}O_5PSi$ 419.2383, found 419.2354.

Allylic Bromide 20. To a solution of **19** (3.0 g, 6.29 mmol) and Et_3N (1.73 mL, 1.26 g, 12.6 mmol) in 30 mL of THF at −60 °C was added MsCl (63 μL, 935 mg, 8.18 mmol). After 30 min, the reaction was warmed to 0 °C for another 30 min. Freshly dried LiBr (5.8 g, 67.1 mmol) in 30 mL of THF was added rapidly by cannula. After 30 min at 0 °C, the reaction was quenched by addition of satd $NaHCO_3$ and extracted 4× with Et_2O. The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated to provide crude **20** (3.06 g, 90% yield) as a yellowish oil and as a mixture of diastereomers: $R_f = 0.44$ (50% EtOAc in hexanes); ^{1}H NMR (300 MHz, C_6D_6) δ 5.38 (t, $J = 5.4$ Hz, 1H), 5.23 (t, $J = 6.6$ Hz, 0.33H), 5.17 (t, $J = 6.6$ Hz, 0.66H), 4.32−4.12 (m, 1H), 4.02−3.86 (m, 4H), 3.70 (d, $J = 8.4$ Hz, 2H), 2.40−1.70 (m, 9H), 1.61 (s, 1H), 1.57 (s, 2H), 1.41−1.25 (m including a singlet at 1.40 and doublet of doublets at 1.29, $J = 17.7$, 7.2 Hz, 6H), 1.10−0.94 (m including singlets at 1.01 and 0.96, 15H), 0.26−0.08 (m including singlets at 0.26, 0.2, 0.18, 0.12, 0,11, 0.08, 6H); IR (neat) 2930, 2856, 1656, 1462, 1250 cm^{-1}; EIMS *m*/*z* 481 (M−Br, 8), 459 (4), 401 (93); HREIMS calcd for $C_{20}H_{38}O_4PSi$ (M$^+$ − *t*Bu − HBr) 401.2277, found 401.2240.

Ketone 21. To a solution of **8** (1.00 g, 2.81 mmol) in 14 mL of THF at −78 °C was added freshly prepared LDA (3.5 mL, 1.0 M, 3.5 mmol). After 20 min, **20** (2.00 g, 3.71 mmol) and freshly dried

(29) The reaction mixture becomes gelatinous so a large stir bar should be used. The reaction has also been performed on a 13 g scale with an overhead stirrer with comparable yields.

(30) Diethyl 3-oxo-2-butylphosphonate is the minor impurity but is removed in the final reaction leading to **27**.

(31) Key ^{1}H NMR signals in C_6D_6 for the product included singlets at 1.70, 1.03, 0.98, 0.20, 0.14, 0.12, 0.10 ppm.

LiI (1.12 g, 8.37 mmol), cooled to −78 °C in 18 mL of THF over 4 Å molecular sieves, was added rapidly by cannula. The solution was warmed to 0 °C and stirred for 2 h and then quenched with ice cold satd $NaHCO_3$ and extracted 3× with Et_2O. The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated. The crude product was frozen in 50 mL of benzene containing Et_3N (∼ 150 μL) and was stored overnight.[32] Evaporation followed by purification by flash chromatography on silica gel (10 to 50% EtOAc in hexanes) provided **21** (1.55 g, 65% yield) as a yellow oil and as a mixture of diastereomers:[33] R_f = 0.43 (50% EtOAc in hexanes); ^{1}H NMR (300 MHz, C_6D_6) δ 5.40−5.20 (m including triplet at 5.34, J = 6.3 Hz, 2H), 4.33−4.18 (m, 1H), 4.10−3.86 (m, 4H), 3.80−3.58 (m, 4H), 2.62 (dd, J = 7.8, 4.2 Hz, 1H), 2.50−1.94 (m including doublet of doublets at 2.43, J = 14.4, 6.3 Hz, 12H), 1.90−1.75 (m, 1H), 1.70 (m including singlets at 1.70, 1.64, 1.61, 8H), 1.44−1.25 (m, including singlets at 1.41, 1.40, 9H), 1.14−0.94 (m including singlets at 1.03, 0.98, 0.96, 39H), 0.21−−0.05 (m including singlets at 0.20, 0.16, 0.14, 0.13, 0.10, 0.06, −0.03, 6H); IR (neat) 2944, 1716, 1644, 1463, 1249 cm^{-1}.

Diol 22. To a solution of **21** (1.40 g, 1.64 mmol) and Et_3N (7.9 mL, 5.7 g, 57 mmol) in 8 mL of CH_2Cl_2 at rt was added TREAT·HF (8.0 mL, 7.92 g, 49.1 mmol). The solution was heated to 45 °C for 36 h then cooled and diluted with CH_2Cl_2. The reaction mixture was washed 3× with H_2O, and the combined aqueous layers were back extracted 3×. The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated. The crude residue was purified by flash chromatography on silica gel (0 to 6% MeOH in EtOAc) to provide **22** (801 mg, 83% yield) as a yellow oil and as a mixture of diastereomers: R_f = 0.25 (3% MeOH in EtOAc); ^{1}H NMR (500 MHz, C_6D_6) δ 5.38−5.22 (m, 2H), 4.18−4.06 (m, 1H), 4.00−3.70 (m, 5H), 3.70−3.46 (m, 3H), 2.80 (dd, J = 9.0, 4.0 Hz, 0.33H), 2.74−2.65 (m, 0.66H), 2.50−2.00 (m including 2 doublets of doublets at 2.47, J = 14.0, 5.5 Hz and 2.40, J = 15.5, 6.0 Hz, 10H), 2.00−1.70 (m, 2H), 1.65−1.45 (m including singlets at 1.62, 1.60, 1.60, 1.54, 8H), 1.44−1.38 (m including singlets at 1.43, 1.42, 1.41, 1.40, 6H), 1.22−1.09 (m, 2.5H), 1.09−0.97 (m, 8.5H); IR (neat) 3407, 2982, 2939, 1705, 1639, 1456, 1217 cm^{-1}; EIMS m/z 584 (M^+, 5), 526 (11); HREIMS calcd for $C_{31}H_{53}O_8P$ 584.3478, found 584.3450.

Ketoaldehyde 23. To a solution of **22** (270 mg, 0.462 mmol) and pyridine (220 μL, 220 mg, 2.77 mmol) in 5 mL of CH_2Cl_2 at rt was added the Dess−Martin periodinane (DMP; 591 mg, 1.40 mmol). The reaction was monitored by TLC, and after 3.5 h an additional portion of DMP (100 mg, 0.237 mmol) was added. After an additional 30 min, the reaction mixture was diluted with EtOAc and washed with a 1:1 solution of satd $Na_2S_2O_3$ and satd $NaHCO_3$. The combined aqueous layer was back extracted 2× with EtOAc, and the combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated. The crude product was purified by flash chromatography on silica gel (0 to 3% MeOH in EtOAc) to provide **23** (220 mg, 82% yield) as a clear oil and as a mixture of diastereomers: R_f = 0.40 (3% MeOH in EtOAc); ^{1}H NMR (300 MHz, C_6D_6) δ 9.34−9.30 (m, 1H), 5.18 (at, J = 6.6 Hz, 2H), 4.00−3.80 (m, 4H), 3.74−3.54 (m, 2H), 3.40−2.90 (m, 3H), 2.60−2.45 (m, 1H), 2.45−2.25 (m, 4H), 2.15−1.75 (m, 8H), 1.62 (s, 3H), 1.55 (s, 3H), 1.41−1.30 (m including doublet at 1.35, J = 6.9 Hz, 9H), 1.02 (dt, J = 6.9, 2.1 Hz, 3H), 1.01 (t, J = 6.9 Hz, 3H), 0.86 (s, 1.5H), 0.85 (s, 1.5H); IR (neat) 2984, 2938, 1 713, 1642, 1455, 1246, 1219 cm^{-1}; EIMS m/z 580 (M^+, 3), 522 (100); HREIMS calcd for $C_{31}H_{49}O_8P$ 580.3165, found 580.3194.

Diketone 24. To a solution of **23** (274 mg, 0.472 mmol) and LiCl (195 mg, 4.72 mmol) in 94 mL of acetonitrile at rt was added diisopropylethylamine (820 μL, 610 mg, 4.72 mmol). After 45 h, the reaction was concentrated, dissolved in CH_2Cl_2, and washed 2× with H_2O. The combined aqueous layer was back extracted 2×, and the combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated. The crude product was purified by flash chromatography on silica gel (5−35% EtOAc in hexanes) to provide **24** (141 mg, 70% yield) as a white powder: decomp 155−161 °C (some decolorization 105−155 °C); R_f = 0.50 (50% EtOAc in hexanes); ^{1}H NMR (500 MHz, C_6D_6) δ 6.44 (t, J = 6.5 Hz, 1H), 5.02−494 (m, 2H), 3.71−3.61 (m, 2H), 2.68 (ddd, J = 13.5, 8.0, 5.0 Hz, 1H) 2.50−2.34 (m, 4H), 2.18−2.06 (m, 3H), 2.06−1.80 (m, 6H), 1.73 (s, 3H), 1.57 (ddd, J = 16.0, 11.5, 8.0 Hz, 1H), 1.7 (s, 3H), 1.51 (s, 3H), 1.43 (s, 3H), 1.404 (s, 3H), 1.395 (s, 3H), 1.05 (s, 3H); ^{13}C NMR (75 MHz, C_6D_6) δ 205.8, 200.2, 153.3, 147.9, 140.2, 138.3, 137.6, 134.1, 122.5, 120.8, 107.0, 58.5, 50.2, 48.2, 40.3, 39.7, 35.1, 34.5, 33.0, 31.0, 25.6, 25.5, 24.1, 17.0, 16.6, 15.7, 12.0; IR (neat) 2972, 2916, 1712, 1661, 1645, 1377 cm^{-1}; EIMS m/z 426 (M^+, 63), 368 (62); HREIMS calcd for $C_{27}H_{38}O_4$ 426.2770, found 426.2767.

Keto Alcohol 25. An aluminate solution was prepared by adding *t*-BuLi (3.2 mL, 1.67 M, 5.34 mmol) to DIBAL (1.0 mL, 798 mg, 5.61 mmol) in 6.5 mL of THF at −98 °C (N_2/MeOH). To a solution of **24** (195 mg, 0.457 mmol) in 11 mL of THF at −98 °C was added the aluminate (800 μL, 0.5M, 0.40 mmol). The reaction was monitored carefully by TLC, and small aliquots (3−4 drops) of aluminate were added until all starting material had been consumed. The reaction was quenched with 500 μL of MeOH and warmed to 0 °C, and 5.0 mL of satd Na_2SO_4 was added. After 20 min, the suspension was filtered through a pad of Celite, rinsing with Et_2O and then subsequently washed 2× with H_2O. The combined aqueous layer was back extracted 2×, and the combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated. The crude residue (4:1, α/β by ^{1}H NMR) was purified by flash chromatography on silica gel (5−65% EtOAc in hexanes) to provide **C11α-25** (145 mg, 74% yield) as a foam: R_f = 0.23 (40% EtOAc in hexanes); ^{1}H NMR (300 MHz, C_6D_6) δ 5.28−5.14 (m, 3H), 4.02 (dd, J = 9.3, 4.2 Hz, 1H), 3.80−3.60 (m, 2H), 2.66 (dd, J = 13.5, 10.8 Hz, 1H), 2.42−2.34 (d br, J = 9.9 Hz, 1H), 2.30−1.58 (m including a triplet at 2.25, J = 5.4 Hz, 13H), 1.54 (s, 3H), 1.49 (s, 3H), 1.46 (s, 3H), 1.44 (s, 3H), 1.41 (s, 3H), 1.08 (s, 3H); ^{13}C NMR (75 MHz, C_6D_6) δ 206.6, 155.0, 147.9, 137.8, 138.2, 133.0, 128.3, 124.3, 122.2, 106.8, 76.3, 58.5, 49.5, 48.7, 40.6, 39.4, 35.2, 33.0, 30.6. 28.9, 25.6, 25.4, 24.2, 16.7, 15.8, 15.2, 10.4; IR (neat) 3400, 2935, 1704, 1642, 1450 cm^{-1}; EIMS m/z 428 (M^+, 27), 389 (5), 370 (7); HREIMS calcd for $C_{27}H_{40}O_4$ 428.2926 found 428.2921. **C11β-25** (39 mg, 20%) was also isolated as a foam: R_f = 0.33 (40% EtOAc in hexanes); ^{1}H NMR (300 MHz, C_6D_6) δ 5.23 (t, J = 5.4 Hz, 1H), 5.31 (t, J = 7.5 Hz, 1H), 5.26−5.16 (m, 1H), 4.06 (dd, J = 9.0, 3.6 Hz, 1H), 3.75−3.58 (m, 2H), 2.45−2.34 (m, 2H), 2.28−1.94 (m, 8H), 1.94−1.62 (m, 6H), 1.56 (s, 3H), 1.50 (s, 3H), 1.44 (s, 3H), 1.43 (s, 3H), 1.42 (s, 3H), 1.22 (s, 3H); ^{13}C (75 MHz, C_6D_6) δ 206.0, 154.9, 147.5, 136.9, 136.5, 134.2, 126.5, 125.6, 122.4, 106.9, 76.1, 58.4, 49.2, 47.8, 40.2, 38.8, 35.6, 33.0, 30.0, 28.3, 25.55, 25.46, 24.4, 17.3, 15.03, 14.99, 11.21; IR (neat) 3447, 2934, 1707, 1643, 1373 cm^{-1}; EIMS m/z 428 (M^+, 6), 410 (4), 370 (5) 352 (4); HREIMS calcd for $C_{27}H_{40}O_4$ 428.2926, found 428.2914.

Ketone 26. To a solution of **25** (78 mg, 0.18 mmol) and Et_3N (175 μL, 128 mg, 1.30 mmol) in 2.0 mL of CH_2Cl_2 at rt was added TESCl (155 μL, 137 mg, 0.910 mmol) dropwise. The reaction was monitored by TLC and after 1.5 h was diluted with CH_2Cl_2 and washed 3× with H_2O. The combined aqueous layer was back extracted 3×, and the combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated. The crude product was purified by flash chromatography on silica gel (1 to 25% EtOAc in hexanes) to provide **26** (83 mg, 84% yield) as a yellow oil: R_f = 0.34 (20% EtOAc in hexanes); ^{1}H NMR (300 MHz, C_6D_6) δ 5.36 (t, J = 4.8 Hz, 1H), 5.28 (dd, J = 10.6, 5.1 Hz, 1H), 5.21 (d, J = 8.4 Hz, 1H), 4.20 (dd, J = 8.7, 4.5 Hz, 1H), 3.76−3.56 (m, 2H), 2.66 (dd, J = 13.8, 10.6 Hz, 1H), 2.43−2.36 (m, 1H), 2.24−1.66 (m, 13H), 1.59 (s, 3H), 1.55 (s, 3H), 1.49 (s, 3H), 1.42 (s,

(32) It was noted that storage overnight in benzene containing Et_3N scavenged the excess allylic iodide, making the purification easier.

(33) Complete stereoselectivity was achieved at C1, as indicated by the formation of a single diastereomer from the macrocyclization.

3H), 1.38 (s, 3H), 1.08−0.97 (m, 12H), 0.70−0.52 (m, 6H); ^{13}C NMR (75 MHz, C_6D_6) δ 206.3, 154.9, 147.9, 137.9, 137.6, 132.8, 127.3, 124.4, 122.2, 106.8, 76.9, 58.5, 49.4, 48.8, 40.8, 39.2, 35.0, 33.0, 31.9, 28.5, 25.7, 25.3, 24.2, 17.0, 16.0, 15.2, 10.6, 7.2, 5.4; IR (neat) 2951, 2913, 2876, 1716, 1647, 1457 cm^{-1}; EIMS *m*/*z* 542 (M^+, 40), 484 (56), 456 (23); HREIMS calcd for $C_{33}H_{54}O_4Si$ 542.3791, found 542.3773.

C23-*β*-Methylketone 27. To a solution of **26** (128 mg, 0.236 mmol) in 7 mL of THF at −78 °C was added freshly prepared LDA (1.18 mL, 1.0M, 1.18 mmol). After 20 min, a THF solution of MeI/HMPA (2:1)[34] was added (1.9 mL, 1.0 M in MeI, 1.9 mmol). After 10 min, the reaction mixture was warmed to −30 °C for 20 min and then 0 °C for 20 min. The reaction was quenched by addition of ice cold satd $NaHCO_3$ and extracted 3× with hexane/Et_2O (1:1). The combined aqueous layer was back extracted 3×, and the combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated. The crude product was purified by flash chromatography on silica gel (5 to 20% EtOAc in hexanes) to provide **27** (127 mg, 97% yield) as a yellowish oil: R_f = 0.38 (20% EtOAc in hexanes); ^{1}H NMR (300 MHz, C_6D_6) δ 5.45 (t, *J* = 4.8 Hz, 1H), 5.35 (dd, *J* = 10.5, 5.4, 1H), 5.27 (d, *J* = 7.5 Hz, 1H), 4.22 (dd, *J* = 8.7, 4.5 Hz, 1H), 3.68 (dd, *J* = 11.7, 4.8 Hz, 1H), 3.58 (dd, *J* = 12.0, 6.9 Hz, 1H), 2.75−2.62 (m, 2H), 2.52−2.38 (m, 1H), 2.32−1.64 (m, 11H), 1.60 (s, 3H), 1.58 (s, 3H), 1.50 (s, 3H), 1.42 (s, 3H), 1.41 (s, 3H), 1.15 (s, 3H), 1.04 (t, *J* = 8.0 Hz, 9H), 0.78 (d, *J* = 7.2 Hz, 3H), 0.65 (q, *J* = 8.0 Hz, 6H); ^{13}C NMR (75 MHz, C_6D_6) δ 206.9, 158.9, 146.0, 137.9, 137.8, 132.7, 127.3, 124.6, 122.1, 106.9, 76.9, 64.1, 49.1, 46.3, 40.8, 39.4, 36.7, 35.1, 31.8, 28.3, 25.9, 25.3, 24.2, 16.9, 15.9, 15.3, 14.6, 10.6, 7.2, 5.4; IR (neat) 2938, 2876, 1715, 1638, 1372 cm^{-1}; EIMS *m*/*z* 556 (M^+, 2), 335 (100); HREIMS calcd for $C_{34}H_{56}O_4Si$ 556.3948, found 556.3951.

C23-α-Methylketone 28. To a solution of **27** (20 mg, 0.036 mmol) and Et_3N (50.0 μL, 28 mg, 0.287 mmol) in 4 mL of CH_2Cl_2 at 0 °C was added TBSOTf (41 μL, 47 mg, 0.179 mmol). After 30 min the reaction was quenched with ice cold satd $NaHCO_3$, diluted with CH_2Cl_2, and extracted twice with satd $NaHCO_3$. The combined aqueous layer was back extracted 3×, and the combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated to provide the crude silyl enol ether as a tan oil: ^{1}H NMR (300 MHz, C_6D_6) δ 5.54−5.36 (m, 3H), 4.26−4.16 (m, 3H), 2.78 (d, *J* = 10.8 Hz, 1H), 2.68 (dd, *J* = 13.2, 10.2 Hz, 1H), 2.42 (ddd, *J* = 17.7, 10.5, 7.5 Hz, 1H), 2.30−1.71 (m, 11H), 1.64 (s, 3H), 1.61 (s, 3H), 1.58 (s, 3H), 1.54 (s, 3H), 1.53 (s, 3H), 1.47 (s, 3H), 1.21 (s, 3H), 1.10−1.01 (m, 18H), 0.67 (q, *J* = 7.8 Hz, 6H), 0.36 (s, 3H), 0.34 (s, 3H). To a solution of crude silyl enol ether in 4 mL of CH_2Cl_2 at −94 °C was added 5 drops of a wet trichloroacetic acid/CH_2Cl_2 solution (2.5 g of TCA in 2 mL of CH_2Cl_2, cooled to −94 °C) every 5 min. The reaction mixture was carefully maintained at −94 °C.[35] As soon as TLC indicated that the silyl enol ether had been completely hydrolyzed (2 h), additional portions of acid were added in the same way for an additional 1 h. The reaction was then quenched by adding Et_3N (250 μL, 182 mg, 1.82 mmol) in 10 mL of CH_2Cl_2 cooled to −94 °C. Warming to 0 °C was followed by addition of CH_2Cl_2 and washing 1× with H_2O and 2× satd $NaHCO_3$. The combined aqueous layer was back extracted 3×, and the combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated to provide crude **28** as a yellow oil: R_f = 0.38 (20% EtOAc in hexanes); ^{1}H NMR (300 MHz, C_6D_6) δ 5.44 (t, *J* = 4.8 Hz, 1H), 5.37 (dd, *J* = 11.0, 4.5 Hz, 1H), 5.25 (d, *J* = 8.7 Hz, 1H), 4.26 (dd, *J* = 9.0, 4.2 Hz, 1H), 3.58 (dd, *J* = 12.3, 2.4 Hz, 1H), 3.33 (dd, *J* = 12.6, 3.6 Hz, 1H), 2.76 (dd, *J* = 13.5, 11.0 Hz, 1H), 2.51 (dd, *J* = 11.4, 3.0 Hz, 1H), 2.40−1.68 (m, 12H), 1.61 (s, 6H), 1.59 (s, 3H), 1.53 (s, 3H), 1.25 (s, 3H), 1.15 (d, *J* = 7.2 Hz, 3H), 1.11−1.02 (m, 12H), 0.69 (q, *J* = 7.8 Hz, 6H); ^{13}C NMR (75 MHz, C_6D_6) δ 206.0, 159.0, 148.7, 138.1, 137.8, 132.8, 127.1, 124.5, 122.1, 103.3, 76.9, 64.7, 49.5, 49.4, 41.0, 39.6, 37.6, 35.0, 31.9, 28.8, 27.8, 24.2, 20.7, 16.8, 16.1, 16.0, 15.2, 10.6, 7.2, 5.5; IR (neat) 2937, 1714, 1646, 1457 cm^{-1}; EIMS *m*/*z* 556 (M^+, 22), 499 (8), 470 (17); HREIMS calcd for $C_{34}H_{56}O_4Si$ 556.3948, found 556.3934. ^{1}H NMR indicated that the stereochemical purity of product was >95%, and TLC indicated that there were only traces of deprotected byproducts. Spectroscopic data was obtained from material that was purified by chromatography (silica gel, 5−20% EtOAc in hexanes); crude material was used in the final step.

(±)-**Terpestacin 1.** To a solution of crude **28** in 3.0 mL of THF at 0 °C was added ice cold 1 N HCl (180 μL, 0.18 mmol). The reaction was monitored and was quenched after 1 h by addition of ice cold satd $NaHCO_3$ and then diluted with EtOAc and washed twice more with satd $NaHCO_3$. The combined aqueous layer was back extracted 3×, and the combined organic extracts washed with brine, dried over Na_2SO_4, and concentrated. The crude product was purified by flash chromatography on silica gel (75% EtOAc in hexanes) to provide **1** (11.5 mg, 79% overall yield from **27**) as a white solid: mp 179−185 °C (some decolorization 120−171 °C); R_f = 0.47 (75% EtOAc in hexanes), R_f = 0.32 (2:1 EtOAc−hexanes + 0.5% HOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.00 (s br, 1H), 5.42−5.37 (m, 1H), 5.24 (dd, *J* = 10.5, 5.5 Hz, 1H), 5.15−5.11 (m, 1H), 4.06 (dd, *J* = 10.0, 4.0 Hz, 1H), 3.88 (dd, *J* = 10.5, 7.0 Hz, 1H), 3.82 (dd, *J* = 10.0, 5.0 Hz, 1H), 2.73−2.62 (m including doublet of doublets at 2.71, *J* = 11.5, 2.0 Hz, 2H), 2.44 (d, *J* = 17.5 Hz, 1H), 2.38 (dd, *J* = 13.5, 10.5 Hz, 1H), 2.30−2.18 (m, 2H), 2.16−1.86 (m, 4H), 1.80−1.63 (m including singlets at 1.64 and 1.63, 10H), 1.57 (s, 3H), 1.29 (d, *J* = 7.0 Hz, 3H), 0.99 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 207.8, 148.7, 146.5, 138.0, 136.5, 132.9, 128.9, 124.3, 121.5, 76.5, 66.1, 49.6, 48.9, 40.3, 39.3, 37.1, 34.9, 29.8, 28.8, 23.8, 16.2, 15.6, 15.3, 14.4, 10.4; IR (neat) 3919 (br), 2932, 1696, 1651, 1455 cm^{-1}; EIMS *m*/*z* 402 (M^+, 23), 384 (24), 366 (2); HREIMS calcd for $C_{25}H_{38}O_4$ 402.2770, found 402.2760.

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Supporting Information Available: General methods and experimental procedures for the preparation of **1**, **4**, **14**, **17** and of all intermediates leading from ***β*-25** to **29** (11-*epi*-terpestacin). Reproductions of ^{1}H and ^{13}C NMR data of **1**, **4**, **24**−**29**, and of the intermediates leading to **29**; reproductions of ^{1}H NMR spectra of **19**−**23** and of the diol precursor to **18**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(34) Iodomethane and HMPA were freshly distilled, and the iodomethane was filtered through basic alumina. The solution was prepared over molecular sieves.

(35) It was necessary to add liquid N_2 approximately every 2.5 min to maintain a temperature of −94 °C.