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Chemo- and Regioselective Functionalization of Nortrilobolide: Application for Semisynthesis of the Natural Product 2-Acetoxytrilobolide

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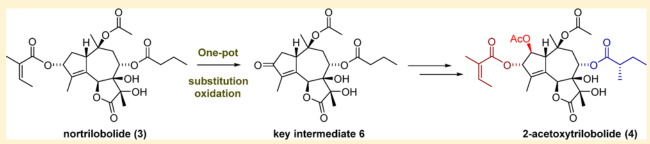
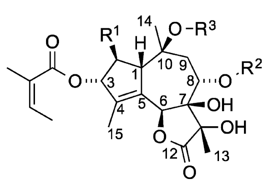
Ⓢ *Supporting Information*

ABSTRACT: The difference in reactivity of the hexaoxygenated natural product thapsigargin (**1**) and the pentaoxygenated nortrilobolide (**3**) was compared in order to develop a chemo- and regioselective method for the conversion of nortrilobolide (**3**) into the natural product 2-acetoxytrilobolide (**4**). For the first time, a stereoselective synthesis of 2-acetoxytrilobolide (**4**) is described, which involves two key reactions: the first chemical step was a one-pot substitution−oxidation reaction of an allylic ester into its corresponding α,β-unsaturated ketone. The second process consisted of a stereoselective α'-acyloxylation of the key intermediate α,β-unsaturated ketone to afford its corresponding acetoxyketone, which was converted into 2-acetoxytrilobolide (**4**) in a few steps. This innovative approach would allow the synthesis of a broad library of novel and valuable penta- and hexaoxygenated guaianolides as potential anticancer agents.



Guaianolides are a class of biologically active sesquiterpernes that have been intensively studied during the last few decades.[1] Among this large family of compounds, hexaoxygenated guaianolides such as thapsigargin (**1**) isolated from *Thapsia garganica* L.[2] and pentaoxygenated guaianolides such as trilobolide (**2**) isolated from *Laser trilobum* (L.) Borkh,[3] as shown in Figure 1, are potent inhibitors of the sarco/endoplasmic reticulum Ca^{2+}-ATPase (SERCA).[4]

Both types of guaianolides have the same binding site in the SERCA pump, but trilobolide (**2**) has a lower affinity than thapsigargin (**1**).[5] The subnanomolar affinity for SERCA has made thapsigargin (**1**) a major tool for investigation of the Ca^{2+} homeostasis in cells.[6] In addition, conjugating thapsigargin (**1**) to peptides has provided recently several prodrugs as efficient treatments of various cancer types such as prostate and liver cancer.[7]



1 Thapsigargin	R^1 = O-Oct	R^2 = But	R^3 = Ac
2 Trilobolide	R^1 = H	R^2 = (*S*)-2-MeBut	R^3 = Ac
3 Nortrilobolide	R^1 = H	R^2 = But	R^3 = Ac
4 2-Acetoxytrilobolide	R^1 = O-Ac	R^2 = (*S*)-2-MeBut	R^3 = Ac
5 2-Hydroxy-10-deacetyltrilobolide	R^1 = OH	R^2 = (*S*)-2-MeBut	R^3 = H

Abbreviations: Oct = Octanoyl, Ac = Acetyl, But = Butanoyl

Figure 1. Absolute configuration of a number of penta- and hexaoxygenated guaianolides.

Hexaoxygenated as well as pentaoxygenated guaianolides can be found in umbelliferous plants (Apiaceae). Until recently hexaoxygenated guaianolides had only been found in the genus *Thapsia*, whereas pentaoxygenated guaianolides such as nortrilobolide (**3**) were known from *Thapsia* and *Laser*.[8] However, Zídek and co-workers have isolated hexaoxygenated 2-acetoxytrilobolide (**4**) and 2-hydroxydeacetyltrilobolide (**5**) from *L. trilobum*, revealing that both *L. trilobum* and *T. garganica* can express the enzyme needed for producing hexaoxygenated guaianolides.[9]

Although biologists quickly acted on the unique properties of thapsigargin (**1**), chemists and biochemists reacted more slowly. Consequently, the guaianolide biosynthesis pathway remains a subject of particular interest. At present, kunzeaol is assumed to be the first monocyclic precursor for the biosynthesis of the guainolide backbone of thapsigargins,[8b,10] but no clear understanding of either formation of the tricyclic guaianolide skeleton or the introduction of the many oxygen atoms on the skeleton exists. In the absence of this significant information on its biosynthesis, the possibility for genetically modifying other organisms to produce the highly oxygenated

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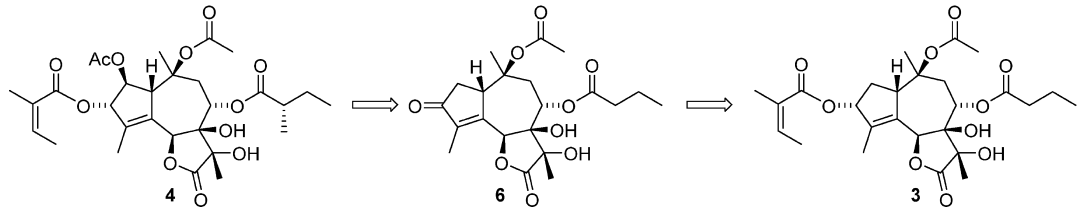
Scheme 1. Retrosynthesis of 2-Acetoxytrilobolide (4) from Nortrilobolide (3)



guaianolide does not yet exist. Several chemical studies have allowed the preparation of thapsigargins, nortrilobolides, and related guaianolides,[1,11] but this has required a tremendous synthetic effort, as exemplified by the total synthesis of thapsigargin (**1**) in 42 steps from (*S*)-carvone published by Ley and co-workers.[11c] However, a possible pathway for accessing the hexaoxygenated guaianolides could be the use of the pentaoxygenated guaianolides as starting materials. To the best of our knowledge, there is no such precedent successful synthetic investigation in the literature. In this present study, the synthesis of 2-acetoxytrilobolide (**4**) from nortrilobolide (**3**) was chosen as a representative example. Although oxygenation of C-2 in nortrilobolide (**3**) is not feasible since this methylene group is not activated, an appropriate transformation of C-3 into a ketone as observed in derivative **6** could possibly allow a stereoselective oxidation of C-2, which should provide 2-acetoxytrilobolide (**4**) after a few subsequent chemical modifications (Scheme 1).

Since angelic acid is an α,β-unsaturated acid, this ester group is the most resistant to saponification among the other esters in thapsigargin (**1**) and trilobolide (**2**). However, several methods have been developed for selective cleavage of this ester by either potassium permanganate or osmium tetraoxide-periodate oxidation in order to get the corresponding pyruvate ester, which could be cleaved selectively by solvolysis in the presence of pyridine in methanol to form the expected 3-alcohol.[12] The 3-alcohol can easily be oxidized into the corresponding 3-ketone.[12b]

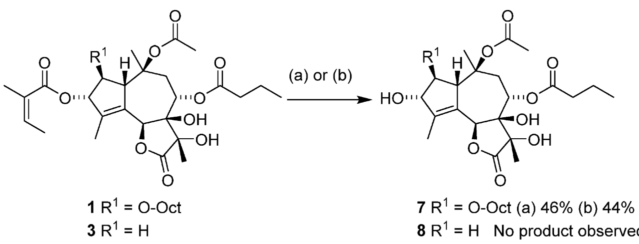
A great number of procedures for α-oxygenation of a carbonyl group have been described including, for example, oxidation with manganese(III) species[13] or other heavy metals,[14] sigmatropic rearrangement of the corresponding acyloxyenamines,[15] hypoiodite-catalyzed α-oxyacylation,[16] or epoxidation of the corresponding trimethylsilyl enol ethers.[11c] In addition, α-halogenation of a ketone[17] followed by substitution with a carboxylate[17b] group might be a possibility. Herein, we wish to report for the first time the synthesis of 2-acetoxytrilobolide (**4**) from nortrilobolide (**3**). The procedure uses a one-pot cleavage of an angelate ester and the oxidation of the alcohol intermediate into its corresponding ketone as well as a stereoselective α'-acyloxylation.

■ RESULTS AND DISCUSSION

As seen in Scheme 2, attempts to selectively remove the angelate ester of nortrilobolide (**3**) employing either the potassium permanganate ($KMnO_4$) or osmium tetraoxide (OsO_4) procedures,[12] which were successful for thapsigargin (**1**), failed due to extensive oxidation of the C-4 double bond in nortrilobolide (**3**), affording a complex mixture.

A milder procedure for the removal of the angelate ester via ozonolysis was then attempted. Ozonolysis of the angelate ester of thapsigargin (**1**) proceeded fairly selectively to afford the corresponding pyruvate ester, which was solvolyzed to give the

Scheme 2. Selective Angelate Cleavage[a]



[a]Reagents and conditions: (a) (1) $KMnO_4$ (4 equiv), $BnEt_3NCl$ (0.08 equiv), toluene, H_2O, rt, 7 h; (2) MeOH, pyridine, H_2O, reflux conditions, 7 h; (b) (1) OsO_4 (0.015 equiv), NMO (1.15 equiv), acetone, H_2O, rt, 4 h; (2) $NaIO_4$ (3 equiv), rt, 16 h; (3) MeOH, pyridine, H_2O, reflux conditions, 16 h.

3-alcohol.[11c] However, the same procedure performed on nortrilobolide (**3**) resulted in the ring-opening of the five-membered ring to afford diketone **9** and acetal **10** in a 1:1 mixture, as depicted in Scheme 3. According to the NMR spectra, only one isomer of **10** was formed, the relative configuration of which was not be determined. The lower reactivity of the C-4 double bond in thapsigargin (**1**) is probably caused by steric hindrance of the octanoyl group in the 2-position, which is not the case in nortrilobolide (**3**).

Hydrazinolysis of angelate esters into their corresponding 3-hydrazinopropionate derivatives followed by spontaneous cyclization to afford the corresponding alcohols has successfully been applied.[18] Indeed, in the case of thapsigargin (**1**), hydrazinolysis furnished the deacylated compound **11**, as shown in Scheme 4. In contrast, hydrazinolysis of nortrilobolide (**3**) afforded a mixture of triol **12** (isomeric mixture of angelate and tiglate ester) and tetraol **13** in a 5:1 ratio. In addition, relactonized product **14** was also observed.

In order to see if tetraol **13** could be used as starting material in an alternative synthetic route to yield **4**, the 8-hydroxy group had to be protected to enable selective oxidation of the 3-hydroxy group. In the case of deacylated derivative **11**, treatment with 2,2-dimethoxypropane in acidified acetone led to the corresponding acetonide in good yield.[12a] Unfortunately, attempts to convert tetraol **13** into acetonide **15** by treatment with 2,2-dimethoxypropane under acidic conditions were not successful, as only the methoxy ketal **16** was isolated in 43% yield, as observed in Scheme 5.

Analogously, **17** formed by deacetylation of **3** by treatment with triethylamine in methanol was converted into a mixture of a minor amount of the 3-angelate ester **18** and a major amount of the 3-methyl ether **16** (in a 1:9 ratio) after treatment with 2,2-dimethoxypropane and acetone under acidic conditions (Scheme 6). The two epimeric methyl ethers **16** were formed in the approximate ratio 1:1.

This unexpected outcome indicated that the substitution at C-3 probably occurred by an S_N1 reaction. Intriguing in this

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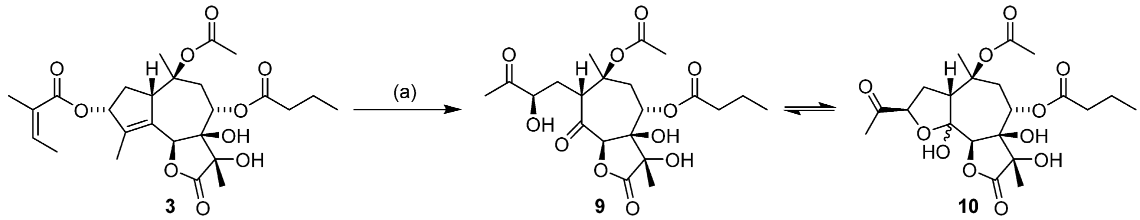
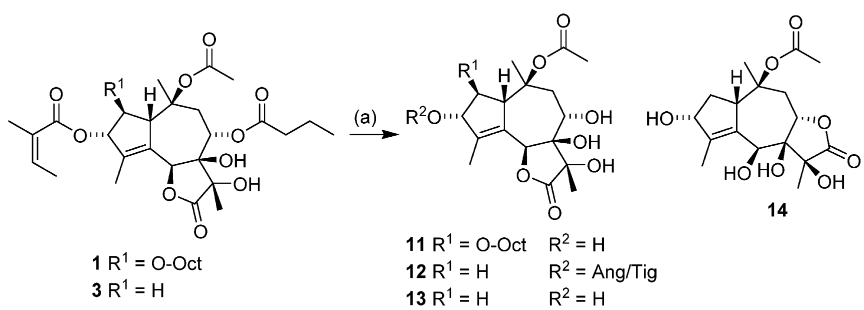
Scheme 3. Ozonolysis of Nortrilobolide (3) Yielding Diketone 9 and Acetal 10[a]



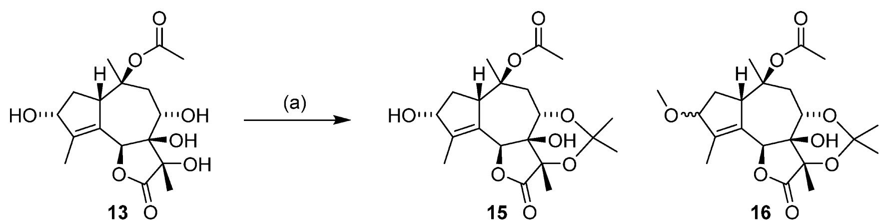
[a]Reagents and conditions: (a) (1) O_3, dichloromethane (DCM), −78 °C, 10 min then PPh_3 (7 equiv), rt, 16 h; (2) MeOH, pyridine, H_2O, reflux conditions, 6 h, 33% (in a 1:1 ratio).

Scheme 4. Hydrazinolysis of Nortrilobolide (3) Yielding Triol 12 and Tetraols 13 and 14[a]



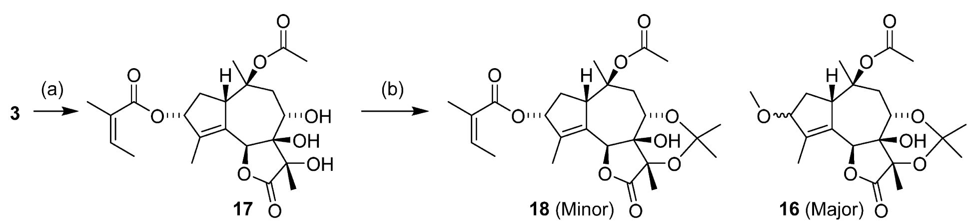
[a]Reagents and conditions: $NH_2NH_2 \cdot H_2O$ (1.26 equiv), EtOH, reflux conditions, 16 h, 35% for **12**, 9% for **13**.

Scheme 5. Acetalation of 13 Yielding Methoxy Ketal 16[a]



[a]Reagents and conditions: (a) 2,2-dimethoxypropane (125 equiv), *p*-TsOH (2 mol %), acetone, 50 °C, 16 h, 43%, dr 1:1.

Scheme 6. Synthesis of Derivatives 16 and 18[a]



[a]Reagents and conditions: (a) TEA (20 equiv), MeOH, rt, 16 h; (b) 2,2-dimethoxypropane (82 equiv), *p*-TsOH (2 mol %), acetone, 50 °C, 16 h, 35% (over two steps, 9:1 ratio).

context is that the corresponding acetalation for *O*-8-debutanoyl thapsigargin could run in excellent yield to give the corresponding angeloyl acetal.[19] These surprising findings suggested that the angelate ester of nortrilobolide (**3**) would be prone to undergo substitution with a hydroxy group in an acidic mixture of water and an organic aprotic solvent. As predicted, treatment of nortrilobolide (**3**) with an acidic mixture of water and acetonitrile did afford the desired 3-alcohol **19** as shown in Table 1. The reactions were performed on a 0.1−1 mmol scale and resulted in yields ranging from 30% to 35%.[20] NMR analysis showed the presence of two alcohols corresponding to a mixture of epimers **19*R*** and **19*S*** in a 1.25:1 ratio. During the optimization of the reaction conditions for the conversion of nortrilobolide (**3**) into the corresponding 3-alcohol **19**, it was found that the presence of water was crucial (entry 1), while a weak acid (pK_a 4−5) required prolonged reaction time (entry 2), and a stronger acid (pK_a −2−0.5) accelerated not only the formation of the allylic alcohol **19** (entries 3−7) but also its decomposition. The reaction was enhanced at high temperature obtained either by heating or by the use of microwave (MW) irradiations (entries 5, 6, and 9). Moreover, at elevated temperatures only a catalytic amount of the acidic medium was needed to achieve high conversion of nortrilobolide (**3**) into the desired product (entry 7). However, the allylic alcohol **19** appeared to be unstable in an acidic medium, explaining the

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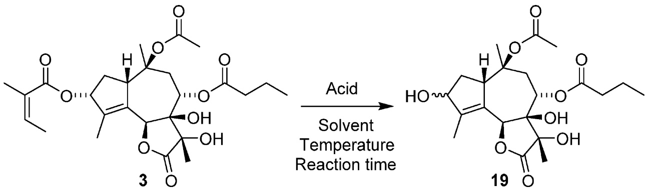
Table 1. Substitution of Angelate Ester of Nortrilobolide (3) under Acidic Aqueous Conditions



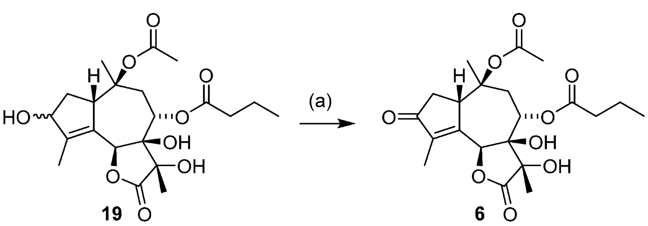
entry	acid (equiv)	temperature (°C)	reaction time (h)	solvent	conversion (%)[e]
1	AcOH (12)	60	2	CH_3CN	0
2	AcOH (3)	60	18	CH_3CN/H_2O[c]	~10
3	p-TsOH (2)	42	18	CH_3CN/H_2O[c]	~50
4	p-TsOH (2)	60	6	CH_3CN/H_2O[d]	~90
5	p-TsOH (2)	100	1	CH_3CN/H_2O[d]	100
6	TFA (5)	80[b]	1	CH_3CN/H_2O[d]	100
7	TFA (0.4)	80	4	CH_3CN/H_2O[d]	~90
8	HF (0.5)[a]	60	16	CH_3CN	~60
9	HF (3)[a]	85[b]	1	CH_3CN	~95

[a]1 M aqueous solution. [b]Under MW irradiations. [c]Ratio CH_3CN-H_2O was 5:1. [d]Ratio CH_3CN-H_2O was 9:1. [e]Reactions were performed on a 0.1−1 mmol scale, and conversion was determined by ^1H NMR analysis of the crude material.

obtained poor yields although the starting material was fully converted.

The epimeric alcohols **19** were successfully oxidized by Dess−Martin periodinane in the presence of pyridine to the corresponding ketone **6** in 87% yield (Scheme 7).

Scheme 7. Oxidation of the Allylic Alcohol 19 into Key-Intermediate Ketone 6[a]

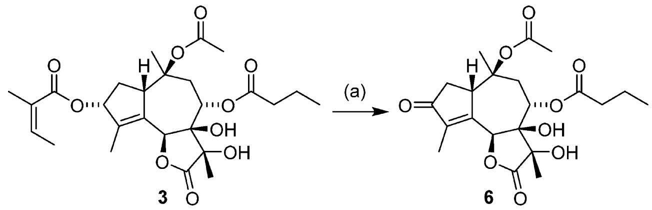


[a]Reagents and conditions: (a) Dess−Martin periodinane (1.5 equiv), pyridine (9 equiv), dry DCM, rt, 2 h, 87%.

With the aim of limiting the degradation of the allylic alcohol intermediate **19** during the angelate cleavage in the acidic medium, a one-pot procedure was developed in order to oxidize in situ the allylic alcohol intermediate **19** into the corresponding ketone **6**. After extensive investigation, it was found that treatment of nortrilobolide (**3**) with chromium(VI) oxide in a mixture of a 1 M aqueous hydrofluoric acid solution and acetonitrile afforded the desired ketone **6** in 74% yield after only 2 h at 95 °C under microwave conditions, as highlighted in Scheme 8.

Importantly, this reaction could be easily performed on a gram scale. To the best of our knowledge, this is an unprecedented procedure for converting an allylic ester into

Scheme 8. One-Pot Two-Step Substitution−Oxidation of 3 into Ketone 6[a]

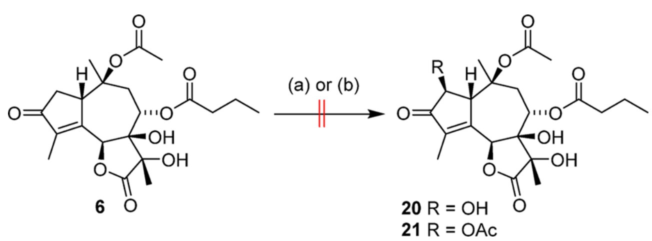


[a]Reagents and conditions: (a) CrO_3 (1.4 equiv), 1 M HF(aq) (2 equiv), CH_3CN, MW, 95 °C, 2 h, 74%.

an α,β-unsaturated ketone. Furthermore, it was demonstrated that a selective cleavage of the angelate ester over the remaining ester functionalities in nortrilobolide (**3**) could be successfully achieved by using this one-pot substitution−oxidation procedure.

With the easy access to the α,β-unsaturated ketone **6**, the next challenge was to introduce an acetoxy group in the α'-position. Preliminary attempts at α'-oxidation of ketone **6** to afford α'-hydroxyketone **20** were performed using the camphor-based oxaziridine methodology developed by Davis and co-workers.[21] Thus, treatment of ketone **6** with freshly prepared lithium diisopropylamide (LDA) (3 equiv) followed by the addition of camphorsulfonyl oxaziridine (2 equiv) did not lead to formation of the expected α'-hydroxyketone **20**. Probably, the two hydroxy groups at the 7- and 11-positions prevented the lithiation of the α'-position. Introduction of an acetoxy group at the α'-position using a recently described procedure[22] on similar complex guaianolides also failed, as shown in Scheme 9.[23] The major difference between **6** and the

Scheme 9. Attempts for the Stereoselective α'-Hydroxylation and α'-Acyloxylation of Ketone 6[a]



[a]Reagents and conditions: (a) LDA (3 equiv), dry THF, −78 °C, 3 h, then (1R)-(−)-(10-camphorsulfonyl)oxaziridine (2 equiv), −78 to −30 °C, 3 h; (b) $KMnO_4$ (2.10 equiv), AcOH (35 equiv), Ac_2O (9.5 equiv), dry benzene, 85 °C, 16 h.

model compounds used in the study mentioned is the presence of an ester in the 8-position, which could explain the difference of reactivity.

Selective α'-acyloxylation of α,β-unsaturated ketones using manganese(III) acetate with a Dean−Stark trap has been reported previously by Demir and co-workers.[13] Therein, it was found that using acetic anhydride as a cosolvent instead of acetic acid did enhance the conversion rates; however, in our particular case acetic acid was much more effective. Thus, treatment of **6** with manganese(III) acetate in a mixture of dry benzene and glacial acetic acid using a Dean−Stark trap to remove the water formed during the reaction resulted in the exclusive formation of α'-acetoxyketone **21** with the desired stereochemistry at C-2, as confirmed by NMR analysis. Indeed,

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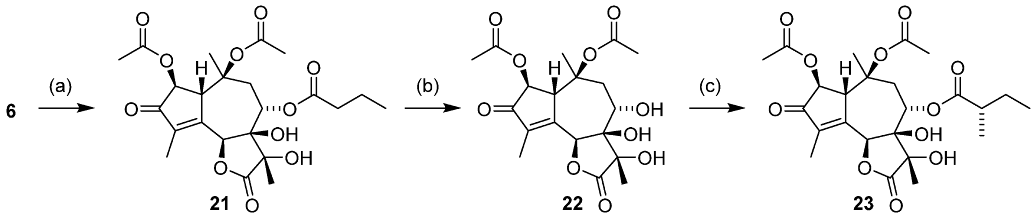
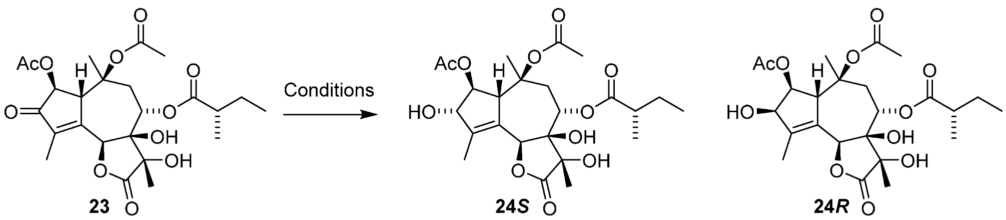
Scheme 10. Formation of 23 from 6[a]



[a]Reaction conditions: (a) $Mn(OAc)_3 \cdot 2H_2O$ (2.15 equiv), AcOH−dry benzene (1:5), Dean-Stark, reflux conditions, 6 h; (b) TEA (26.5 equiv), MeOH, 60 °C, 30 min, 57% (over two steps); (c) (*S*)-2-methylbutyric anhydride (4 equiv), 4-dimethylaminopyridine (DMAP) (1 mol %), THF, rt, 1 h, 78%.

Table 2. Attempts at the Stereoselective Reduction of Acetoxyketone 23 into Alcohols 24*R* and 24*S*



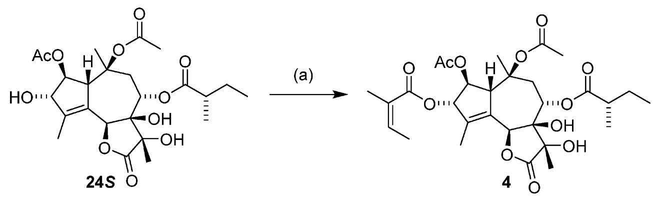
conditions	dr (24*S*/24*R*)	yield (%)
$NaBH_4$, MeOH, 0 °C	1:2	37
$CeCl_3 \cdot 7H_2O$, MeOH then $NaBH_4$, −60 °C	1:8	60
$Zn(BH_4)_2$, THF, −30 °C → 10 °C, 16 h (with EDTA workup)	1:1.85	61

ROESY experiments showed a correlation between H-2 and H-14 (for more details, see the Supporting Information). Methanolysis of α'-acetoxyketone **21** in the presence of triethylamine in methanol[12b] was easily achieved to afford the desired *O*-8-debutanoyl 2-acetoxyketone (**22**) (57% yield over two steps from ketone **6**), which was successfully esterified to give the (*S*)-methylbutanoate derivative **23** at O-8 in 78% yield, as seen in Scheme 10.

Stereoselective reduction of similar ketones to give the α-alcohols has previously been performed using zinc borohydride.[11c,24] Thus, the 2-acetoxyketone **23** was converted into the two separable epimeric alcohols **24*R*** and **24*S*** after treatment with zinc borohydride and the use of an ethylenediaminetetraacetic acid (EDTA) workup. However, a selectivity of approximately 2:1 toward the undesired *syn*-diastereomer **24*R*** (3β-alcohol) was obtained, as depicted in Table 2.

A chelation of zinc to both the C-3 ketone and the carbonyl group of the acetyl moiety might explain the observed outcome of this reduction. Due to the flexibility of the acetyl group at C-2, the hydride might approach preferentially from the α-face, resulting in the undesired *syn*-product **24*R*** as the major product. The same unfavorable ratio of isomers was observed when sodium borohydride was used. Premixing ketone **23** with cerium(III) chloride prior to the addition of sodium borohydride did not improve the selectivity in favor of the desired **24*S*** derivative; on the contrary, the selectivity was enhanced toward the undesired **24*R*** derivative. In spite of this unwanted selectivity of the reaction, the procedure is still attractive since the unwanted alcohol **24*R*** can be oxidized to ketone **23**, which then can be recycled for preparation of the 3α-alcohol **24*S***.[25] Finally, angeloylation of alcohol **24*S*** under Yamaguchi conditions led to the desired 2-acetoxytrilobolide (**4**) in 49% yield (Scheme 11).

Scheme 11. Angeloylation of 24*S* to Afford 2-Acetoxytrilobolide (4)[a]



[a]Reagents and conditions: (a) 2,4,6-trichlorobenzoyl chloride (2 equiv), TEA (2 equiv), angelic acid (2 equiv), toluene, 75 °C, 48 h, 49%.

Comparison of the synthesized 2-acetoxytrilobolide (**4**) with the reported isolated sample of the natural product confirmed the correct stereochemistry at C-2 and C-3 (for more details, see the Supporting Information).

The functionalization of the hexaoxygenated thapsigargin (**1**) has previously been intensively studied in our group. Application of the same chemical conditions to nortrilobolide (**3**) has resulted in a clear difference of reactivity between these two classes of derivatives. Based on these findings a protocol for selective cleavage of the angelate ester in nortrilobolide (**3**) has been successfully applied. Furthermore, a one-pot procedure for the substitution−oxidation reaction for converting nortrilobolide (**3**) into the key-intermediate ketone **6** has been developed. This might be a general procedure for converting allylic esters into their corresponding α,β-unsaturated ketones. Combined with a highly stereoselective α'-acetoxylation of **6** on C-2, a semisynthesis of 2-acetoxytrilobolide (**4**) has been successfully completed in six steps from nortrilobolide (**3**). These valuable outcomes could provide an expedient access to a wide library of analogues of trilobolides and related thapsigargins. The synthesis of new hexaoxygenated

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guaianolides and their biological evaluations are currently in progress in our laboratory.

■ EXPERIMENTAL SECTION

General Experimental Procedures. A crude extract containing nortrilobolide (**3**) was received from GenSpera (San Antonio, TX, USA) and purified by dry column vacuum chromatography on silica gel using DCM−EtOAc (5:1) as eluent (R_f = 0.23) prior to use. All solvents and reagents were obtained from commercial suppliers and used without further purification unless otherwise stated. All air- and moisture-sensitive reactions were conducted under argon using oven- or flame-dried glassware and in dried solvents according to standard procedures. Reactions were followed by thin-layer chromatography (TLC) using precoated aluminum plates and visualized using vanillin reagent (15 g of vanillin, 250 mL of EtOH, and 2.5 mL of conc H_2SO_4). Flash column chromatography was performed with silica gel (35−75 μm). Dry column vacuum chromatography was carried out with silica gel (20−45 μm). Optical rotations were measured as $[\alpha]_D$ values (c in g/100 mL). Yields refer to isolated compounds estimated to be >95% pure as determined by ^{1}H NMR spectroscopy. NMR spectra were recorded on 400 and 600 MHz instruments. The chemical shifts (δ) are given in parts per million (ppm) relative to residual signals of the solvent ($CDCl_3$ and CD_3OD). Coupling constants (J values) are given in hertz (Hz). Multiplicities of ^{1}H NMR signals are reported as follows: s, singlet; d, doublet; dd, doublet of doublets; dt, doublet of triplets; ddd, doublet of doublets of doublets; dtt, doublet of triplets of triplets; t, triplet; m: multiplet; q, quartet; dq, doublet of quartets; qq, quartet of quartets; b, broad signal. Assignments of the NMR signals were made using 1D (^{1}H, ^{13}C, DEPTQ) and 2D (COSY, HSQC, HMBC, ROESY) spectra. Microwave-assisted synthesis was carried out in a Biotage Initiator apparatus operating in single mode; the microwave cavity produced controlled irradiation at 2.45 GHz. The reactions were run in sealed vessels. These experiments were performed by employing magnetic stirring and a fixed hold time using variable power to reach the desired temperature (for 1−2 min) and then maintained at the desired temperature in the vessel for the programmed time period. The temperature was monitored by an IR sensor focused on a point on the reactor vial glass. The IR sensor was calibrated to internal solution reaction temperature by the manufacturer. HRMS data were recorded on a micrOTOF-Q instrument using electrospray (ESI) as ionization method.

Ozonolysis of Nortrilobolide (3). Ozone was bubbled through a solution of nortrilobolide (**3**) (0.30 g, 0.59 mmol) in dry DCM (100 mL) at −78 °C for 10 min until the solution turned pale blue. The solution was first flushed with oxygen for 10 min, then flushed with nitrogen for 10 min before Ph_3P (1.10 g, 4.19 mmol) was added to the solution and stirred at room temperature overnight. The solution was concentrated under reduced pressure, and the crude product was purified through a short plug of silica gel using toluene−EtOAc (3:1 to 2:1) as eluent before it was dissolved in dry MeOH (50 mL) and treated with pyridine (5 mL) and H_2O (5 mL). The reaction mixture was stirred under reflux for 6 h, cooled to room temperature, and quenched by the addition of a saturated aqueous NH_4Cl solution (100 mL). The aqueous phase was extracted with DCM (3 × 50 mL), and the combined organic phases were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by dry vacuum column chromatography on silica gel using toluene−EtOAc (3:1 to 2:1) as eluent to afford diketone **9** and acetal **10** (0.09 g, 33%) in a 1:1 ratio as a pale yellow oil. An analytically pure sample of compound **9** was obtained as a pale yellow oil: ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.45 (1H, d, J = 4.8 Hz, H-8), 5.06 (1H, s, OH), 4.96 (1H, s, H-6), 4.15 (1H, d, J = 11.2 Hz, H-1), 4.08 (1H, dt, J = 8.3, 4.1 Hz, H-3), 3.94 (1H, s, OH), 3.82 (1H, s, OH), 2.97 (1H, d, J = 15.1 Hz, H-9a), 2.67 (1H, dd, J = 15.4, 5.9 Hz, H-9b), 2.61 (1H, ddd, J = 13.4, 11.3, 4.4 Hz, H-2a), 2.23 (3H, s, H-15), 2.18−2.04 (2H, m, butanoyl H-2), 2.00 (3H, s, acetyl CH_3), 1.68 (1H, ddd, J = 13.6, 8.1, 2.1 Hz, H-2b), 1.56 (3H, s, H-13), 1.54−1.48 (2H, m, butanoyl H-3), 1.29 (3H, s, H-14), 0.87 (3H, t, J = 7.4 Hz, butanoyl H-4); ^{13}C NMR (101 MHz, $CDCl_3$) δ 209.8 (C-4), 200.5 (C-5), 176.1 (C-12), 172.4 (butanoyl C═O), 170.7 (acetyl C═O), 85.8 (C-6), 82.1 (C-10), 78.8 (C-11), 76.3 (C-7), 74.7 (C-3), 70.3 (C-8), 50.1 (C-1), 36.5 (C-9), 36.1 (butanoyl C-2), 29.5 (C-2), 25.4 (C-15), 22.6 (acetyl CH_3), 22.5 (C-14), 21.9 (C-13), 17.7 (butanoyl C-3), 13.7 (butanoyl C-4); HRMS m/z 499.1794 $[M + Na + H_2O]^+$, calcd for $C_{21}H_{32}O_{12}Na$ 499.1791. An analytically pure sample of compound **10** was obtained as a pale yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.57 (1H, t, J = 3.8 Hz, H-8), 5.23 (1H, s, H-6), 4.60 (1H, t, J = 8.7 Hz, H-3), 4.50 (1H, s, OH), 4.15 (1H, s, OH), 3.40 (1H, t, J = 5.4 Hz, H-1), 3.04 (1H, s), 2.86 (1H, dd, J = 14.9, 3.3 Hz, H-9a), 2.52−2.39 (3H, m, H-2, H-9b), 2.30−2.22 (5H, m, H-15, butanoyl H-2), 1.99 (3H, s, acetyl CH_3), 1.70−1.55 (2H, m, butanoyl H-3), 1.52 (3H, s, H-14), 1.47 (3H, s, H-13), 0.93 (3H, t, J = 7.4 Hz, butanoyl H-4); ^{13}C NMR (101 MHz, $CDCl_3$) δ 209.4 (C-4), 175.6 (C-12), 172.4 (butanoyl C═O), 170.1 acetyl C═O), 104.9 (C-5), 84.2 (C-10), 84.0 (C-3), 80.4 (C-6), 79.5 (C-11), 76.6 (C-7), 66.6 (C-8), 56.9 (C-1), 38.8 (C-9), 36.7 (butanoyl C-2), 28.6 (C-2), 26.2 (C-15), 22.7 (acetyl CH_3), 22.1 (C-14), 18.1 (butanoyl C-3), 16.56 (C-13), 13.9 (butanoyl C-4); HRMS m/z 499.1781 $[M + Na + H_2O]^+$, calcd for $C_{21}H_{32}O_{12}Na$ 499.1791.

Hydrazinolysis of Nortrilobolide (3). To a solution of nortrilobolide (**3**) (1.00 g, 1.97 mmol) in absolute EtOH (30 mL) was added hydrazine hydrate (0.12 mL, 2.47 mmol) at room temperature under an argon atmosphere. The reaction mixture was stirred under reflux for 16 h, then cooled to room temperature. The reaction was concentrated, and the resulting crude material was purified by flash column chromatography on silica gel using gradient elution (toluene−EtOAc, 2:1 to 1:2) to furnish triol **12**[5] as a pale yellow solid (0.31 g, 35%), tetraol **13** as a pale yellow solid (0.06 g, 9%), and relactonized tetraol **14** (0.01 g, 1%) as a pale yellow solid. Compound **13**: ^{1}H NMR (600 MHz, CD_3OD) δ 5.83−5.80 (1H, m, H-6), 4.53−4.46 (1H, m, H-3), 4.33 (1H, t, J = 3.6 Hz, H-8), 4.21−4.16 (1H, m, H-1), 2.93 (1H, dd, J = 14.0, 3.5 Hz, H-9a), 2.36−2.28 (2H, m, H-9b, H-2a), 1.99 (3H, s, acetyl CH_3), 1.93 (3H, s, H-15), 1.58 (1H, ddd, J = 13.4, 8.0, 6.9 Hz, H-2b), 1.41 (3H, s, H-14), 1.40 (3H, s, H-13); ^{13}C NMR (151 MHz, CD_3OD) δ 177.6 (C-12), 172.12 (acetyl C═O), 145.5 (C-5), 130.7 (C-4), 88.0 (C-10), 80.43 (C-7/C-11), 80.37 (C-7/C-11), 79.4 (C-6), 78.2 (C-3), 70.2 (C-8), 51.5 (C-1), 41.1 (C-9), 35.8 (C-2), 22.45 (bs, acetyl CH_3, C-14), 16.4 (C-13), 12.8 (C-15); HRMS m/z 379.1366 $[M + Na]^+$, calcd for $C_{17}H_{24}O_8Na$ 379.1363. Compound **14**: ^{1}H NMR (600 MHz, CD_3OD) δ 5.06 (1H, dd, J = 13.4, 3.3 Hz, H-8), 4.68 (1H, s, H-6), 4.42 (1H, t, J = 6.9 Hz, H-3), 3.56 (1H, t, J = 6.9 Hz, H-1), 2.62 (1H, dd, J = 15.5, 3.3 Hz, H-9a), 2.29 (1H, dt, J = 13.2, 7.7 Hz, H-2a), 2.05−2.01 (1H, m, H-9b), 2.03 (3H, s, acetyl CH_3), 1.95 (3H, s, H-15), 1.58 (3H, s, H-13), 1.50 (1H, ddd, J = 13.4, 7.5, 6.2 Hz, H-2b), 1.44 (3H, s, H-14); ^{13}C NMR (151 MHz, CD_3OD) δ 180.0 (C-12), 172.3 (acetyl C═O), 143.9 (C-5), 135.5 (C-4), 84.59 (C-8), 83.8 (C-10), 80.1 (C-7/C-11), 78.6 (C-3), 77.2 (C-7/C-11), 70.8 (C-6), 49.2 (C-1), 40.4 (C-9), 35.5 (C-2), 24.4 (C-14), 23.6 (C-13), 22.2 (acetyl CH_3), 12.7 (C-15); HRMS m/z 379.1361 $[M + Na]^+$, calcd for $C_{17}H_{24}O_8Na$ 379.1363.

Methoxy Ketal 16. To a solution of tetraol **13** (40 mg, 0.11 mmol) in dry acetone (2 mL) were added 2,2-dimethoxypropane (1.7 mL, 13.8 mmol) and p-TsOH (2 mg, 2 mol %) at room temperature under an argon atmosphere. The reaction was stirred at 50 °C overnight, cooled to room temperature, and quenched by the addition of a saturated aqueous $NaHCO_3$ solution (20 mL). The aqueous phase was extracted with EtOAc (3 × 20 mL), and the combined organic phases were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by dry vacuum column chromatography on silica gel using toluene−EtOAc (5:1) as eluent to lead to a mixture of epimeric methyl ethers **16** (20 mg, 43%) in a 1:1 (R/S) ratio as a pale yellow solid. An analytically pure sample of compound **16*R*** was obtained as a pale yellow solid: ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.82 (1H, s, H-6), 4.27 (1H, dd, J = 4.7, 2.9 Hz, H-8), 4.13 (1H, dt, J = 8.9, 4.5 Hz, H-3), 3.88 (1H, dtt, J = 9.3, 4.7, 2.3 Hz, H-1), 3.38 (3H, s, OCH_3), 2.99 (1H, dd, J = 14.8, 4.5 Hz, H-9a), 2.35−2.31 (1H, m, H-9b), 2.31−2.25 (1H, m, H-2a), 1.98 (3H, s, acetyl CH_3), 1.95 (3H, s, H-15), 1.55−1.53 (7H, m, H-2a, H-13, $C(CH_3)$-(CH_3)), 1.41 (3H, s, $C(CH_3)$-(CH_3)), 1.35 (3H, s, H-14);

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^{13}C NMR (151 MHz, $CDCl_3$) δ 173.2 (C-12), 170.8 (acetyl-C═O), 143.9 (C-5), 127.4 (C-4), 101.1 (*C*(CH_3)-(CH_3)), 86.3 (C-10), 86.1 (C-3), 79.4 (C-7/C-11), 78.8 (C-6), 76.3 (C-7/C-11), 66.3 (C-8), 56.9 (OCH_3), 50.8 (C-1), 38.5 (C-9), 32.3 (C-2), 30.7 (C(CH_3)-(CH_3)), 23.8 (C(CH_3)-(CH_3)), 22.7 (CH_3CO), 21.2 (C-14), 16.1 (C-13), 12.7 (C-15); HRMS *m/z* 433.1826 $[M + Na]^+$, calcd for $C_{21}H_{30}O_8Na$ 433.1833. An analytically pure sample of compound **16S** has been obtained as a pale yellow solid: ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.77 (1H, s, H-6), 4.24 (1H, dd, *J* = 4.6, 2.9 Hz, H-8), 4.13−4.05 (2H, m, H-3, H-1), 3.31 (3H, s, OCH_3), 2.79 (1H, dt, *J* = 14.7, 3.8 Hz, H-9a), 2.52 (1H, dt, *J* = 14.6, 2.1 Hz, H-9b), 1.99 (6H, s, H-15, acetyl CH_3), 1.98−1.94 (1H, m, H-2a), 1.85−1.76 (1H, 1H, H-2b), 1.53 (3H, s, H-13), 1.52 (3H, s, C(CH_3)-(CH_3)), 1.40 (3H, s, C(CH_3)-(CH_3)), 1.30 (3H, s, H-14); ^{13}C NMR (151 MHz, $CDCl_3$) δ 173.3 (C-12), 170.5 (acetyl-C═O), 142.5 (C-5), 130.9 (C-4), 100.9 (*C*(CH_3)-(CH_3), 88.9 (C-3), 85.8 (C-10), 79.6 (C-7/C-11), 78.7 (C-6), 76.2 (C-7/C-11), 66.2 (C-8), 56.5 (OCH_3), 53.8 (C-1), 39.1 (C-9), 31.1 (C-2), 30.7 (C(CH_3)-(CH_3)), 23.8 (C(CH_3)-(CH_3)), 22.6 (CH_3CO), 20.3 (C-14), 16.2 (C-13), 14.5 (C-15); HRMS *m/z* 433.1830 $[M + Na]^+$, calcd for $C_{21}H_{30}O_8Na$ 433.1833.

Acetonide 18.[11c] To a solution of nortrilobolide (**3**) (1.00 g, 1.97 mmol) in dry MeOH (100 mL) was added TEA (5.5 mL, 39.5 mmol) at room temperature under an atmosphere of argon. The reaction was stirred at room temperature for 4 h before it was quenched by the addition of an aqueous saturated NH_4Cl solution (100 mL). The aqueous phase was extracted with EtOAc (3 × 100 mL), and the combined organic phases were washed with brine (150 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford the crude triol **17**, which was used in the next reaction without further purification. An analytically pure sample of compound **17**[5] was obtained as a white solid: HRMS *m/z* 461.1767 $[M + Na]^+$, calcd for $C_{22}H_{30}O_9Na$ 461.1782. To a solution of crude **17** (1.97 mmol) in dry acetone (20 mL) were added 2,2-dimethoxypropane (20 mL, 163 mmol) and *p*-TsOH (cat.) at room temperature under an argon atmosphere. The reaction was stirred at 50 °C overnight, cooled to room temperature, and quenched by the addition of a saturated aqueous $NaHCO_3$ solution (50 mL). The aqueous phase was extracted with EtOAc (3 × 100 mL), and the combined organic phases were washed with brine (100 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by dry vacuum column chromatography on silica gel using toluene−EtOAc (5:1) as eluent to provide a mixture of **16** and acetonide **18** (0.33 g, 35%) in a 9:1 ratio as a pale yellow solid. An analytically pure sample of compound **18** has been obtained as a pale yellow solid: ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.11 (1H, q, *J* = 7.3 Hz, angeoyl H-3), 5.84 (1H, s, H-6), 5.57−5.51 (1H, m, H-3), 4.31−4.26 (1H, m, H-8), 4.03−3.96 (1H, m, H-1), 3.19 (1H, s, OH), 2.94 (1H, dd, *J* = 14.6, 4.7 Hz, H-9a), 2.54 (1H, dt, *J* = 13.5, 7.7 Hz, H-2a), 2.42 (1H, dd, *J* = 14.7, 2.9 Hz, H-9b), 2.03−1.99 (3H, m, angeoyl H-4), 1.95 (3H, s, angeoyl 2-CH_3), 1.93−1.89 (6H, m, acetyl CH_3, H-15), 1.61−1.56 (1H, m, H-2b), 1.55 (3H, s, H-13), 1.53 (3H, s, C(CH_3)-(CH_3)), 1.42 (3H, s, C(CH_3)-(CH_3)), 1.36 (3H, s, H-14); ^{13}C NMR (151 MHz, $CDCl_3$) δ 173.3 (C-12), 170.8 (angeoyl C═O), 168.0 (acetyl C═O), 140.9 (C-4), 138.8 (angeoyl C-3), 129.9 (C-5), 127.9 (angeoyl C-4), 101.1 (*C*(CH_3)-(CH_3), 85.7 (C-10), 79.9 (C-3), 79.5, 78.8 (C-6), 76.2, 66.2 (C-8), 51.6 (C-1), 38.4 (C-9), 33.3 (C-2), 30.7 (C(CH_3)-(CH_3)), 23.8 (C(CH_3)-(CH_3)), 22.6 (angeoyl 2-CH_3), 20.9 (C-14), 20.8 (acetyl CH_3), 16.1 (C-13), 12.8 (C-15); HRMS *m/z* 501.2101 $[M + Na]^+$, calcd for $C_{25}H_{34}O_9Na$ 501.2095.

Allylic Alcohol 19. To a solution of nortrilobolide (**3**) (100 mg, 0.2 mmol) in a mixture of MeCN−H_2O (6 mL, 5:1) was added *p*-TsOH (60 mg, 0.32 mmol) at room temperature. The reaction mixture was stirred at 60 °C for 6 h, cooled to room temperature, diluted with EtOAc (30 mL), and washed with water (until pH ∼6). The organic phase was then washed with brine (30 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel using toluene−EtOAc (4:1) as eluent to afford a mixture of epimeric alcohols **19** (63 mg, 75%) in a 1.25:1 (*R/S*) ratio as a pale yellow solid. An analytically pure sample of compound **19*R*** was obtained as a pale yellow solid: ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.69 (1H, s, H-6), 5.61 (1H, t, *J* = 3.6 Hz, H-8), 4.59 (1H, t, *J* = 6.8 Hz, H-3), 4.16 (1H, t, *J* = 7.1 Hz, H-1), 3.08 (1H, dd, *J* = 15.0, 3.5 Hz, H-9a), 2.52 (1H, s, OH), 2.40 (1H, dt, *J* = 13.5, 8.2 Hz, H-2a), 2.27 (3H, t, *J* = 6.8 Hz, butanoyl H-2), 2.22 (1H, dd, *J* = 14.8, 3.9 Hz, H-9b), 1.97 (3H, s, acetyl CH_3), 1.95 (3H, s, H-15), 1.79 (1H, s), 1.69−1.53 (3H, m, H-2b, butanoyl H-3), 1.49 (3H, s, H-13), 1.34 (3H, s, H-14), 0.95 (3H, t, *J* = 7.4 Hz, butanoyl H-4); ^{13}C NMR (151 MHz, $CDCl_3$) δ 176.2 (C-12), 172.9 (butanoyl C═O), 171.3 (acetyl C═O), 146.4 (C-5), 129.1 (C-4), 86.3 (C-10), 78.9 (C-7/C-11), 78.2 (C-6), 77.7 (C-3), 66.7 (C-8), 50.1 (C-1), 38.8 (C-9), 36.8 (butanoyl C-2), 34.7 (C-2), 22.6 (acetyl CH_3), 22.5 (C-14), 18.1 (butanoyl C-3), 16.3 (C-13), 13.9 (butanoyl C-4), 12.9 (C-15); HRMS *m/z* 449.1767 $[M + Na]^+$, calcd for $C_{21}H_{30}O_9Na$ 449.1782. An analytically pure sample of compound **19S** was obtained as a pale yellow solid: ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.61 (1H, s, H-6), 5.59 (1H, t, *J* = 4.0 Hz, H-8), 4.56 (1H, d, *J* = 7.5 Hz, H-1), 4.51 (1H, bs, H-3), 3.48 (1H, s, OH), 3.09 (1H, dd, *J* = 14.8, 3.6 Hz, H-9a), 2.42 (1H, s, OH), 2.25 (2H, t, *J* = 7.6 Hz, butanoyl H-2), 2.19−2.09 (2H, m, H-9b, H-2a), 1.97 (6H, s, H-15, acetyl CH_3), 1.81 (1H, ddd, *J* = 14.7, 8.1, 2.5 Hz, H-2b), 1.67−1.58 (2H, m, butanoyl H-3), 1.50 (3H, s, H-13), 1.21 (3H, s, H-14), 0.94 (3H, t, *J* = 7.4 Hz, butanoyl H-4); ^{13}C NMR (151 MHz, $CDCl_3$) δ 176.4 (C-12), 172.9 (butanoyl C═O), 171.3 (acetyl C═O), 147.0 (C-5), 130.8 (C-4), 86.5 (C-10), 80.1 (C-3), 79.0 (C7/C11), 78.8 (C7/C11), 78.2 (C-6), 66.7 (C-8), 51.7 (C-1), 39.1 (C-9), 36.8 (butanoyl C-2), 35.1 (C-2), 22.5 (acetyl CH_3), 21.9 (C-14), 18.1 (butanoyl C-3), 16.3 (C-13), 14.1 (butanoyl C-4), 13.9 (C-15); HRMS *m/z* 449.1784 $[M + Na]^+$, calcd for $C_{21}H_{30}O_9Na$ 449.1782.

Ketone 6. *Procedure A.* Dess−Martin periodinane (180 mg, 0.42 mmol) was added portionwise to a solution of allylic alcohol **19** (120 mg, 0.28 mmol) in dry DCM (10 mL) and pyridine (0.2 mL, 2.5 mmol) at room temperature under an argon atmosphere. The reaction mixture, which immediately turned dark brown, was stirred for 2 h at room temperature. The resulting yellow solution was quenched by addition of a saturated aqueous $Na_2S_2O_3$ solution (5 mL) and a saturated aqueous $NaHCO_3$ solution (5 mL). The aqueous phase was extracted with EtOAc (3 × 20 mL), and the combined organic phases were washed with brine (30 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by dry vacuum column chromatography on silica gel using toluene−EtOAc (2:1) as eluent to furnish ketone **6** (104 mg, 87%) as a white solid: $[\alpha]^{22}_{D}$ −4 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.81 (1H, s, H-6), 5.71 (1H, t, *J* = 3.7 Hz, H-8), 4.76 (1H, bs, H-1), 4.13 (1H, s, OH), 3.32 (1H, dd, *J* = 14.8, 3.7 Hz, H-9a), 3.13 (1H, s, OH), 2.43 (1H, dd, *J* = 19.5, 6.3 Hz, H-2a), 2.34 (1H, dd, *J* = 19.1, 2.8 Hz, H-2b), 2.27 (2H, t, *J* = 7.5 Hz, butanoyl H-2), 2.09 (1H, dd, *J* = 14.7, 3.8 Hz, H-9b), 1.98 (3H, s, acetyl C═O)), 1.92 (3H, dd, *J* = 2.2, 1.3 Hz, H-15), 1.69−1.54 (2H, m, butanoyl H-3), 1.50 (3H, s, H-13), 1.20 (3H, s, H-14), 0.93 (3H, t, *J* = 7.4 Hz, butanoyl H-4); ^{13}C NMR (151 MHz, $CDCl_3$) δ 207.3 (C-3), 174.8 (C-12), 172.7 (butanoyl C═O), 171.3 (acetyl C═O), 159.4 (C-5), 145.0 (C-4), 85.3 (C-10), 79.3 (C-7/C-11), 78.8 (C-7/C-11), 77.8 (C-6), 66.4 (C-8), 46.2 (C-1), 39.1 (C-9), 36.74 (C-2/butanoyl C-2), 36.69 (C-2/butanoyl C-2), 22.5 (acetyl CH_3), 22.1 (H-14), 18.1 (butanoyl C-3), 16.3 (C-13), 13.8 (butanoyl C-4), 9.9 (C-15); HRMS *m/z* 425.1834 $[M + H]^+$, calcd for $C_{21}H_{29}O_9$ 425.1806.

Procedure B. To a MW vial containing a solution of nortrilobolide (**3**) (1.05 g, 2.07 mmol) was successively added a 1 M aqueous solution of hydrogen fluoride (4.14 mL, 4.14 mmol) and chromium(VI) oxide (290 mg, 1.40 mmol) at room temperature. The MW vial was sealed and heated under MW irradiation for 2 h at 95 °C. After cooling to room temperature, the reaction mixture was diluted with water (70 mL) and extracted with EtOAc (60 mL). The organic layer was successively washed with water, a 2 M aqueous solution of $NaHCO_3$, and brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting off-white solid was purified by column chromatography on silica gel using EtOAc−heptane (1:1) as eluent to afford ketone **6** (651 mg, 74%) as a white solid with spectroscopic data in accordance with previous characterizations.

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***O*-8-Debutanoyl 2-Acetoxyketone (22).** A solution of ketone **6** (230 mg, 0.54 mmol) and manganese triacetate dihydrate (310 mg, 1.16 mmol) in dry benzene−glacial acetic acid (45 mL, 5:1) was stirred under reflux using a Dean−Stark apparatus. After 6 h, the dark color of the solution disappeared and the reaction mixture was diluted with EtOAc (30 mL) and washed with brine (30 mL). The separated organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford the crude 2-acetoxyketone **21** as a yellow solid, which was used in the subsequent reaction without any further purification. An analytically pure sample of compound **21** was obtained as a pale yellow solid: $[\alpha]^{22}_{D}$ − 91.4 (*c* 0.35, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.82 (1H, 1H, H-6), 5.68 (1H, t, *J* = 3.8 Hz, H-8), 5.18 (1H, d, *J* = 3.6 Hz, H-2), 4.60−4.56 (1H, m, H-1), 4.09 (1H, s, OH), 3.23 (1H, dd, *J* = 14.9, 3.7 Hz, H-9a), 3.12 (1H, s, OH), 2.27 (2H, t, *J* = 7.3 Hz, butanoyl H-2), 2.23 (1H, dd, *J* = 14.7, 3.9 Hz, H-9b), 2.09 (3H, s, acetyl$_{C\text{-}2}$ CH_3), 2.01−1.97 (3H, m, H-15), 1.94 (3H, s, acetyl$_{C\text{-}10}$ CH_3), 1.66−1.58 (2H, m, butanoyl H-3), 1.47 (3H, s, H-13), 1.38 (3H, s, H-14), 0.94 (3H, t, *J* = 7.4 Hz, butanoyl H-4); ^{13}C NMR (151 MHz, $CDCl_3$) δ 201.5 (C-3), 175.0 (C-12), 172.8 (butanoyl C═O), 171.2 (acetyl$_{C\text{-}10}$ C═O), 170.2 (acetyl$_{C\text{-}2}$ C═O), 156.7 (C-5), 142.1 (C-4), 84.1 (C-10), 79.1 (C-7/C-11), 78.7 (C-7/C-11), 78.0 (C-6), 73.5 (C-2), 66.2 (C-8), 51.8 (C-1), 38.8 (C-9), 36.7 (butanoyl C-2), 23.0 (C-14), 22.6 (acetyl$_{C\text{-}10}$ CH_3), 20.7 (acetyl$_{C\text{-}2}$ CH_3), 18.1 (butanoyl C-3), 16.2 (C-13), 13.8 (butanoyl C-4), 10.4 (C-15); HRMS *m*/*z* 505.1682 $[M + Na]^+$, calcd for $C_{23}H_{30}O_{11}Na$ 505.1680. To a solution of crude 2-acetoxyketone **21** (0.54 mmol) in dry MeOH (20 mL) was added TEA (2 mL, 14.3 mmol) at room temperature under an atmosphere of argon. The reaction mixture was stirred at 60 °C for 30 min before it was concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel using toluene−EtOAc (2:1) to afford the *O*-8-debutanoyl 2-acetoxyketone (**22**) (63 mg, 57% over two steps from **6**) as a white solid: ^{1}H NMR (600 MHz, CD_3OD) δ 6.07 (1H, s, H-6), 5.22 (1H, d, *J* = 3.5 Hz, H-2), 4.67−4.64 (1H, m, H-1), 4.38 (1H, t, *J* = 3.6 Hz, H-8), 3.13 (1H, dd, *J* = 14.3, 3.7 Hz, H-9a), 2.36 (1H, dd, *J* = 14.3, 3.5 Hz, H-9b), 2.11 (3H, s, acetyl$_{C\text{-}2}$ CH_3), 1.99−1.98 (3H, m, H-15), 1.97 (3H, s, acetyl$_{C\text{-}10}$ CH_3), 1.47 (3H, s, H-14), 1.44 (3H, s, H-13); ^{13}C NMR (151 MHz, CD_3OD) δ 203.8 (C-3), 176.5 (C-12), 172.0 (acetyl$_{C\text{-}10}$ C═O), 171.4 (acetyl$_{C\text{-}2}$ C═O), 160.6 (C-5), 141.1 (C-4), 85.9 (C-10), 80.8 (C-7/C-11), 80.2 (C-7/C-11), 79.1 (C-6), 75.2 (C-2), 69.8 (C-8), 53.0 (C-1), 40.8 (C-9), 23.1 (C-14), 22.6 (acetyl$_{C\text{-}10}$ CH_3), 20.6 (acetyl$_{C\text{-}2}$ CH_3), 16.3 (C-13), 10.1 (C-15); HRMS *m*/*z* 435.1264 $[M + Na]^+$, calcd for $C_{19}H_{24}O_{10}Na$ 435.1262.

(*S*)-Methylbutanoate (23). To a solution of *O*-8-debutanoyl 2-acetoxyketone (**22**) (70 mg, 0.17 mmol) in dry THF (1 mL) were added successively (*S*)-(+)-2-methylbutyric anhydride (130 mg, 0.7 mmol) in dry THF (0.5 mL) and DMAP (2 mg, 0.016 mmol), at room temperature under an argon atmosphere. The reaction mixture was stirred for 1 h at room temperature, then diluted with EtOAc (10 mL) and washed successively with a 2 M aqueous H_2SO_4 solution (5 mL), a saturated aqueous $NaHCO_3$ solution (10 mL), and brine (10 mL). The organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by dry vacuum column chromatography on silica gel using toluene−EtOAc (2:1) as eluent to furnish the (*S*)-methylbutanoate (**23**) (65.5 mg, 78%) as a white solid:[26] $[\alpha]^{22}_{D}$ −40 (*c* 0.3, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.80 (1H, s, H-6), 5.69 (1H, t, *J* = 3.7 Hz, H-8), 5.18 (1H, d, *J* = 3.4 Hz, H-2), 4.64−4.60 (1H, m, H-1), 4.26 (1H, s, OH), 3.27 (1H, dd, *J* = 14.8, 3.7 Hz, H-9a), 3.24 (1H, s, OH), 2.33 (1H, q, *J* = 6.9 Hz, 2-methyl butanoyl H-2), 2.18 (1H, dd, *J* = 14.7, 3.7 Hz, H-9b), 2.09 (3H, s, acetyl$_{C\text{-}2}$ CH_3), 1.98 (3H, s, H-15), 1.94 (3H, s, acetyl$_{C\text{-}10}$ CH_3), 1.73−1.64 (1H, m, 2-methyl butanoyl H-3a), 1.47 (3H, s, H-13), 1.46−1.40 (1H, m, 2-methyl butanoyl H-3b), 1.38 (3H, s, H-14), 1.13 (3H, d, *J* = 7.0 Hz, 2-methyl butanoyl 2-CH_3), 0.90 (3H, t, *J* = 7.5 Hz, 2-methyl butanoyl H-4); ^{13}C NMR (151 MHz, $CDCl_3$) δ 201.5 (C-3), 175.6 (2-methyl butanoyl C═O), 175.1 (C-12), 171.2 (acetyl$_{C\text{-}10}$ C═O), 170.2 (acetyl$_{C\text{-}2}$ C═O), 156.9 (C-5), 142.1 (C-4), 84.2 (C-10), 79.1 (C-7/C-11), 78.6 (C-7/C-11), 78.0 (C-6), 73.4 (C-2), 66.2 (C-8), 51.7 (C-1), 41.6 (2-methyl butanoyl C-2), 38.8 (C-9), 26.3 (2-methyl butanoyl C-3), 23.2 (C-14), 22.6 (acetyl$_{C\text{-}10}$ CH_3), 20.7 (acetyl$_{C\text{-}2}$ CH_3), 16.4 (2-methyl butanoyl 2-CH_3), 16.2 (C-13), 11.8 (2-methyl butanoyl C-4), 10.4 (C-15); HRMS *m*/*z* 519.1843 $[M + Na]^+$, calcd for $C_{24}H_{32}O_{11}Na$ 519.1837.

Alcohol 24*S*. To a solution of (*S*)-methylbutanoate (**23**) (24 mg, 0.048 mmol) in freshly distilled THF (2 mL) was cannulated a precooled solution of zinc borohydride (3.5 mL of a 0.5 M solution in Et_2O, 1.75 mmol) at −30 °C. After stirring the solution for a further 2 h at −30 °C, an additional quantity of zinc borohydride (1 mL of a 0.5 M solution in Et_2O, 0.5 mmol) solution was added. The reaction mixture was allowed to warm to 10 °C and stirred overnight. The reaction mixture was diluted with EtOAc (30 mL) and quenched by the slow addition of an aqueous EDTA solution (30 mL, 30% w/w). The biphasic system was vigorously stirred at room temperature for 2 h. The separated aqueous phase was extracted with EtOAc (3 × 30 mL). The combined organic phases were washed with brine (50 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by dry vacuum column chromatography on silica gel using toluene−EtOAc (2:1) as eluent to afford a mixture of epimeric alcohols **24** (14.6 mg, 61%) in a 1.85:1 (*R*/*S*) ratio as a white solid. An analytically pure sample of compound **24*S*** was obtained as a white solid: ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.67−5.61 (2H, m, H-6, H-8), 4.92 (1H, dd, *J* = 4.8, 3.3 Hz, H-2), 4.46−4.44 (1H, m, H-3), 4.34−4.32 (1H, m, H-1), 3.44 (1H, s, OH), 3.21 (1H, dd, *J* = 14.8, 3.6 Hz, H-9a), 2.70 (1H, s, OH), 2.39−2.29 (2H, m, 2-methyl butanoyl H-2, OH), 2.24 (1H, dd, *J* = 14.8, 3.9 Hz, H-9b), 2.10 (3H, s, acetyl CH_3), 1.96−1.94 (3H, m, H-15), 1.93 (3H, s, acetyl CH_3), 1.75−1.64 (1H, m, 2-methyl butanoyl H-3a), 1.50 (3H, s, H-13), 1.46−1.41 (1H, m, 2-methyl butanoyl H-3b), 1.40 (3H, s, H-14), 1.14 (3H, d, *J* = 7.0 Hz, 2-methyl butanoyl 2-CH_3), 0.91 (3H, t, *J* = 7.5 Hz, 2-methyl butanoyl H-4); ^{13}C NMR (151 MHz, $CDCl_3$) δ 175.5 (2-methyl butanoyl C═O), 175.1 (C-12), 172.9 (acetyl C═O), 170.3 (acetyl C═O), 144.8 (C-5), 126.6 (C-4), 84.9 (C-10), 84.6 (C-2), 83.7 (C-3), 79.0 (C-7/C-11), 78.7 (C-7/C-11), 77.1 (C-6), 66.4 (C-8), 55.6 (C-1), 41.6 (2-methyl butanoyl C-2), 38.5 (C-9), 26.3 (2-methyl butanoyl C-3), 23.6 (C-14), 22.6 (acetyl CH_3), 21.1 (acetyl CH_3), 16.5 (C-13), 16.3 (2-methyl butanoyl 2-CH_3), 13.1 (C-15), 11.8 (2-methyl butanoyl C-4); HRMS *m*/*z* 521.1996 $[M + Na]^+$, calcd for $C_{24}H_{34}O_{11}Na$ 521.1993.

2-Acetoxytrilobolide (4).[9] 2,4,6-Trichlorobenzoyl chloride (9.4 μL, 0.06 mmol) and TEA (8.4 μL, 0.06 mmol) were added successively to a solution of angelic acid (6 mg, 0.06 mmol) in dry toluene (100 μL) at room temperature under an argon atmosphere. The resulting mixture was stirred for 2 h and then treated with alcohol **24*S*** (15 mg, 0.03 mmol). The reaction mixture was stirred at 75 °C for 2 days, then cooled to room temperature and quenched by the addition of a saturated aqueous NH_4Cl solution (3 mL). The aqueous phase was extracted with EtOAc (2 × 5 mL), and the combined organic phases were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by dry vacuum column chromatography on silica gel using toluene−EtOAc (3:1) as eluent to lead to the desired natural product **4** (8.5 mg, 49%) as a colorless oil: ^{1}H NMR (600 MHz, CD_3OD) δ 6.19 (1H, qq, *J* = 7.2, 1.5 Hz, angeoyl H-3), 5.72−5.69 (2H, m, H-3, H-6), 5.62 (1H, t, *J* = 3.7 Hz, H-8), 5.51 (1H, dd, *J* = 4.1, 2.9 Hz, H-2), 4.40−4.36 (1H, m, H-1), 3.01 (1H, dd, *J* = 14.6, 3.7 Hz, H-9a), 2.36 (1H, q, *J* = 6.9 Hz, 2-methyl butanoyl H-2), 2.31 (1H, dd, *J* = 14.6, 3.9 Hz, H-9a), 2.09 (3H, s, acetyl CH_3), 2.01 (3H, dq, *J* = 7.2, 1.5 Hz, angeoyl H-4), 1.94 (3H, p, *J* = 1.5 Hz, angeoyl 2-CH_3), 1.91 (3H, s, acetyl CH_3), 1.88−1.86 (3H, m, H-15), 1.76−1.71 (1H, m, 2-methyl butanoyl H-3a), 1.52−1.46 (1H, m, 2-methyl butanoyl H-3b), 1.45 (3H, s, H-14), 1.38 (3H, s, H-13), 1.17 (3H, d, *J* = 7.1 Hz, 2-methyl butanoyl 2-CH_3), 0.95 (3H, t, *J* = 7.5 Hz, 2-methyl butanoyl H-4); ^{13}C NMR (151 MHz, CD_3OD) δ 178.1 (C-12), 176.2 (2-methyl butanoyl C═O), 171.9 (acetyl C═O), 171.7 (acetyl C═O), 168.7 (angeoyl C═O), 141.0 (C-5), 139.4 (angeoyl C-3), 133.3 (C-4), 128.8 (angeoyl C-2), 85.9 (C-10), 85.6 (C-3), 79.6 (C-2), 79.5 (C-11), 79.4 (C-7), 78.0 (C-6), 67.4 (C-8), 58.9 (C-1), 42.7 (2-methyl butanoyl C-2), 39.5 (C-9), 27.3 (2-methyl butanoyl C-3), 23.5 (C-14), 22.6 (acetyl CH_3), 21.1 (acetyl CH_3), 20.7 (angeoyl 2-CH_3), 16.7 (2-methyl butanoyl 2-CH_3), 16.0 (angeoyl C-

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4), 15.9 (C-13), 13.0 (C-15), 12.0 (2-methyl butanoyl C-4); HRMS m/z 603.2394 $[M + Na]^+$ calcd for $C_{29}H_{40}O_{12}Na$ 603.2412.

■ ASSOCIATED CONTENT

Supporting Information

Copies of ^1H, ^{13}C, HCOSY, HSQC, HMBC, and ROESY NMR spectra of selected compounds. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.jnatprod.5b00333.

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Notes

The authors declare no competing financial interest.

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(25) For similar oxidation of allylic alcohol on related structures, see ref 11c.

(26) A trace amount of (*S*)-(+)-2-methylbutyric anhydride was observed in the NMR spectra.

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