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# STAT-3 Inhibitory Bisabolanes from *Carthamus glaucus*

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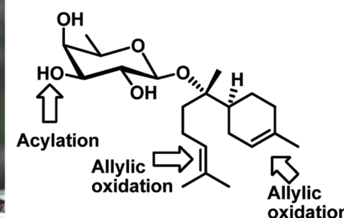
Supporting Information

**ABSTRACT:** Apart from a large amount (ca. 2.0%) of α-bisabolol β-D-fucopyranoside (**2a**), the aerial parts of the Mediterranean weed *Carthamus glaucus* afforded an unusual triglyceride (*E*-2-crotonyl-1,3-distearolylglycerol, **7**), two lipophilic flavonoids (**6a**,**b**), and a series of bisabolane fucopyranosides variously acylated on the sugar moiety (**2b**−**e**) or oxidized on the terpenoid core (**3**, **4a**,**b**, **5a**,**b**). The fucopyranoside **2a** is more soluble in polar media and more versatile in terms of formulation than its aglycone [(−)-α-bisabolol, **1**], an anti-inflammatory cosmetic ingredient in current short supply in its natural form. A comparative investigation of the activity of α-bisabolol (**1a**), the fucopyranoside **2a**, and its senecioate **2b** on transcription factors involved in inflammation and cancer pathways (NF-κB and STAT-3) showed only marginal activity on NF-κB inhibition for all compounds, while STAT-3 was inhibited potently by the fucoside **2a** and, to a lesser extent, also by α-bisabolol. These observations qualify **2a** as an easily available compound, both as an apoptotic lead structure and as a potential alternative to natural α-bisabolol (**1**) for pharmaceutical and/or cosmetic development.




*Carthamus* (family Asteraceae) is an economically important genus endemic to the Mediterranean area encompassing only 14 species.[1] The most important member of the genus is *C. tinctorius* L. (safflower), one of the oldest crops and the source of an edible oil as well as of a red dye (carthamin, CI Natural Red 26), a complex methylidene(bis)chalcone.[2] Safflower is better known as an edible rather than a medicinal plant, but biomedical interest in the species has been rekindled by the breeding of transgenic varieties for the production of mammalian peptides ("pharming"), with safflower-derived human insulin currently undergoing phase II clinical trials in both the U.S. and Europe.[3] The chemical hallmark of the genus *Carthamus* is the accumulation of fucosidated bisabolane sesquiterpenoids,[4] a trait that, curiously, is lacking in safflower. α-Bisabolol (**1**), the major anti-inflammatory agent from chamomile oil, is an important cosmetic ingredient, for which the supply has attracted considerable interest.[5] Chamomile is not an economically viable source of this compound, which is currently obtained from the essential oil (candeia oil) of some South American *Vanillosmopsis* species (*V. pohlii*, *V. arborea*).[5] The production of α-bisabolol from these sources has been questioned, being associated with the destruction of the Mata Atlantica rainforest,[5,6] so the major producer of bisabolol has recently announced it will stop using this source and hence commercializing natural α-bisabolol.[6] Most α-bisabolol on the market is currently obtained by synthesis, either from farnesol, a known skin allergen, or from nerolidol and other terpenoid-building blocks (Symrise[7] and BASF processes[8]). While natural α-bisabolol (**1**) is diastereo- and enantiomerically pure, its synthetic versions are either a racemic mixture (Bisabolol F) or a mixture of a pair of racemic diastereomers (Bisabolol rac). All four stereoisomer of α-bisabolol occur in nature, but racemic α-bisabolol has been reported to be only half as active as natural (−) bisabolol, suggesting that the (+) enantiomer has little, if any, biological activity.[9]

Recently, α-bisabolol has also attracted considerable attention as an apoptotic and chemopreventive agent,[10] prompting us to investigate the distribution of its fucosides in plants from the genus *Carthamus*, the only natural source of

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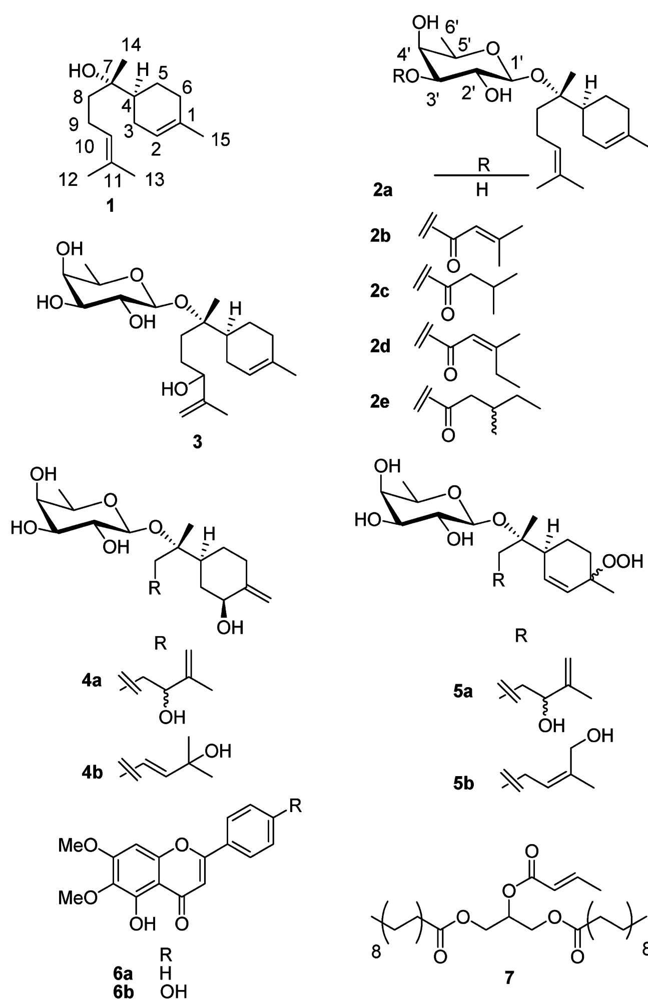
this type of compounds. We report herein that *C. glaucus* M. Bieb., an invasive weed from Eastern Anatolia and the Middle East, is an exceptionally rich source of $\alpha$-bisabolol fucoside (**2a**), and we describe the structure elucidation of the minor constituents of this plant as well as a comparative investigation of the activity of $\alpha$-bisabolol (**1**), the fucoside **2a**, and its senecioyl derivative **2b** against two transcription factors involved in inflammation, thus identifying STAT3 as a selective target of **2a** and **2b**.



## ■ RESULTS AND DISCUSSION

Extraction of the aerial parts of *C. glaucus* with acetone afforded a crude extract (ca. 7% yield), which was partitioned by solid-phase extraction on RP18 silica gel into methanol and acetone eluates, with the sesquiterpene glycosides partitioning selectively into the methanol eluate. The latter was further purified by a quick gravity column chromatography step on silica gel to afford the fucopyranoside **2a** in overall 2.1% yield from the dried plant material. From less and more polar fractions, a host of analogues as well as a pair of lipophilic flavonoids were obtained by a combination of gravity column chromatography, flash chromatography, HPLC, and crystallization. The less polar fractions contained four new analogues of **2a** characterized by acylation of the fucopyranoside moiety (**2b**−**e**), while the more polar ones contained the five oxygenated derivatives **3**, **4a**,**b**, and **5a**,**b**, resulting from the allylic oxidation of one or both of the trisubstituted double bonds of the $\alpha$-bisabolol moiety of **2a**. With the exception of the oxygenated analogue **3**,[11] all the other compounds are new.

The $^{1}$H NMR spectra of the acylated analogues **2b**−**e** were all very similar to that of **2a**,[4] differing only in the presence of the additional signals of an acyl moiety and the marked downfield shift of one of the fucopyranoside oxymethines. For all these compounds, the COSY experiment was used to elucidate the proton multiplets into the bisabolane, the fucopyranoside, and the acyl moiety spin systems, being instrumental to identify *O*-3′ as the esterificaton site. Indeed, the corresponding oxymethine (H-3′) resonated as a double doublet at $\delta_H$ 3.59 in **2a** and at $\delta_H$ 4.88 or 4.89 in **2b**−**e**. This assignment was further supported by the $^{3}J$ HMBC correlations of H-3′ with the acyl carbonyl (C-1″, $\delta_C$ 171.3 in **2b**) and of both the anomeric oxymethine (H-1′, $\delta_H$ 4.48 in **2b**, d, $J$ = 6.8 Hz) and the methyl-bearing oxymethine (H-5′, $\delta_H$ 3.66) with C-3′ ($\delta_C$ 74.6) (the assignment of carbon atoms was obtained by the HSQC experiment). The HMBC experiment also confirmed the presence of the pyranoside form of fucose (HMBC correlation between H-1′ and C-5′), for which the absolute configuration was assumed to be D by analogy with that of **2a**, an assumption in accordance also with the exclusive occurrence of the enantiomeric L-fucose in animals and bacterial tissues.[12]

The acyl moieties bound at C-3′ were identified as senecic acid (**2b**), its homologue *Z*-3-methyl-2-pentenoyl acid (**2d**), and their corresponding dihydro derivatives (**2c** and **2e**, respectively).[13] The double-bond configuration for the acyl moiety of **2d** was established as *Z* on the basis of the NOE interaction between the sp$^{2}$ methine ($\delta_H$ 5.80) and the allylic methyl group ($\delta_H$ 2.20). On the other hand, the configuration of the stereogenic carbon in the side chain of **2e** could not be assessed, but the possible biogenetic derivation of this acid from isoleucine would suggest an *R*-configuration. Acylation is very rare within sesquiterpene fucosides, although a 2′-acyl derivative of a eudesmane fucoside has been reported from *C. lanatus*.[14]

The structures of the more polar analogues **3**, **4a**,**b**, and **5a**,**b** were characterized by the allylic oxidation of one or both of the double bonds of the $\alpha$-bisabolol moiety of **2a**, and their structure elucidation was guided by comparison of their spectroscopic data with those reported for compounds **2a**[4] and **3**.[11] Compound **4a**, $C_{21}H_{36}O_7$ by HRESIMS, was identified as an analogue of compound **3** showing allylic oxygenation also at the endocyclic double bond. Indeed, all the $^{1}$H and $^{13}$C NMR resonances of the fucopyranoside and of the acyclic portion of the $\alpha$-bisabolol moiety were practically coincident with those reported for **3**, while consistent changes occurred in the resonances attributed to the cyclic portion of the sesquiterpene moiety. In particular, $^{1}$H and $^{13}$C NMR resonances of this region, interpreted with the help of 2D COSY and HSQC experiments, showed signals of an exocyclic double bond ($\delta_H$ 4.90 and 4.70, both broad singlets, $\delta_C$ 102.8) of an sp$^{3}$ oxymethine ($\delta_H$ 3.99, $\delta_C$ 71.6), in addition to three sp$^{3}$ methylenes and one sp$^{3}$ methine. The COSY experiment arranged the proton resonances of this moiety within a single spin system going from the oxymethine (H-2) to an allylic methylene resonating at $\delta_H$ 2.03 ($H_2$-6) and encompassing the methine H-4. The $^{3}J$ HMBC cross-peaks of $H_2$-15 with C-1, C-2, and C-6 and those of H-4 with C-2, C-14, and C-8 fully supported the planar structure of compound **4a**. The NOE contact of H-4 with H-2 indicated the *S*-configuration at C-2, while the configuration at C-10 has been left undetermined. Similar to **4a**, compound **5a**, $C_{21}H_{36}O_8$ by HRESIMS, differed from **3** only by the oxidation of the endocyclic double bond. Accordingly, the $^{1}$H and $^{13}$C NMR spectra of these two

compounds differed significantly only for the resonances attributable to the carbocyclic moiety. The COSY spectrum was used to arrange the proton signals of this ring within a single spin system encompassing the mutually coupled $sp^2$ methines H-2 ($\delta_H$ 5.56) and H-3 ($\delta_H$ 6.19), in turn coupled to $sp^3$ methine H-4, and ending with the $sp^3$ methylenes $H_2$-5 and $H_2$-6. Having associated all the proton resonances to those of the directly linked carbon atoms through the HSQC spectrum, the methyl singlet at $\delta_H$ 1.29 ($H_3$-15) could be attached at C-1 on the basis of its 2D HMBC cross-peaks with the oxygenated and unprotonated carbon C-1 ($\delta_C$ 78.7), with the $sp^2$ carbon C-2 ($\delta_C$ 134.0), and with C-6. The molecular formula of **5a** implied that the single oxygenated carbon (of this moiety), namely, C-1, should bear two oxygen atoms, thus indicating the attachment of a hydroperoxy group at this carbon. The 2D NMR ROESY spectrum provided no unambiguous evidence to assess the configuration at C-1, which was thus left undetermined.

The two remaining oxidized bisabolane fucosides, **4b** and **5b**, are structurally related to **4a** and **5a**, respectively, from which they differ only in the acyclic portion of the sesquiterpene moiety. Compound **4b** showed the same molecular formula as **4a**, but the $^1$H and $^{13}$C NMR spectra of these two compounds, while practically superimposable for signals attributed to the sugar and to the carbocyclic moiety, showed marked differences in the H/C resonances attributable to positions from C-8 to C-13. The $^1$H NMR spectrum of **4b** showed the presence of two mutually coupled $sp^2$ methines (H-10 and H-9), linked to an allylic diasterotopic methylene ($\delta_H$ 2.42 and 2.29) through the COSY spectrum, and of a 6H singlet at $\delta_H$ 1.28. The 2D HMBC spectrum of **4b** allowed the attachment of these moieties with the fucoside linking carbon C-7 and with the oxygenated carbocyclic ring and fully clarified the structure of this compound. In particular, H-4 showed cross-peaks with the oxygenated C-2, with C-14, and with the allylic C-8; $H_2$-8 showed key cross-peaks with C-14 and C-4; and finally, $H_3$-12/$H_3$-13 ($\delta_H$ 1.28) showed cross-peaks with C-13/C-12, with the oxygenated and unprotonated C-11 ($\delta_C$ 70.8), and with the $sp^2$ carbon C-10 ($\delta_C$ 137.5). The coupling constant $J_{H\text{-}9/H\text{-}10}$ = 15.1 Hz indicated the *E*-configuration at the $\Delta^9$ double bond. Similarly, compound **5b** showed the same molecular formula as **5a**, but marked differences in the H/C NMR resonances attributable to positions from C-8 to C-13. The structure of this portion of the sesquiterpene moiety of **5b** was identified on the basis of the following spectroscopic evidence: (i) the COSY spectrum of **5b** showed a sequence of a $sp^2$ methine (H-10) and two $sp^3$ methylenes ($H_2$-9 and $H_2$-8); (ii) the remaining signals of this portion were an oxygenated methylene (AB system at $\delta_H$ 4.10 and 4.05) and a methyl singlet ($\delta_H$ 1.74); (iii) both these groups were attached at the $sp^2$ carbon C-11 on the basis of the HMBC cross-peaks of $H_2$-12 with C-11, C-13, and C-10 and of $H_3$-13 with C-12, C-11, and C-10; and (iv) the NOE contact of $H_3$-13 with H-10 indicated the *Z* geometry of the $\Delta^{10}$ double bond. Finally, this acyclic portion was attached at the hydroperoxylated six-membered ring though the HMBC cross-peaks of $H_2$-8 with the fucoside-linking C-7, with C-14, and C-4, thus completely defining the structure of **5b**. The occurrence of an allylic hydroperoxide moiety in **5a**,**b** suggests derivation from the ene-type reaction of **2a** with a singlet oxygen equivalent. The "random" oxygenation pattern raises concerns over the natural product state of these compounds, which were, nevertheless, isolated from all the collections of the plant under investigation. Remarkably, photooxygenation of **2a** afforded hydroperoxides exclusively derived from attack at the $\Delta^1$ double bond,[15] while three different patterns of oxidation at the $\Delta^{10}$ double bond were found (oxygen bound at C-10 in **3**, **4a**, and **5a**, at C-11 in **4b**, and at C-12 in **5b**), suggesting the involvement of an enzymatic step in their genesis.

All the fucopyranosides were obtained as amorphous gums, and the purification of the two co-occurring lipophilic flavonoids mosloflavone (**6a**)[16] and cirsimaritin (**6b**)[17] greatly benefited from their crystalline state and easy precipitation from crude fractions dissolved in ether.

The acetone eluate from the solid-phase extraction step was fractionated by GCG to afford, apart from taraxasterol, the unusual triglyceride **7**. The NMR spectra of this compound ($C_{43}H_{80}O_6$, HRMS) showed signals diagnostic of a symmetrically substituted glyceride backbone [oxymethine at $\delta$ 5.32 (m), oxymethylenes at $\delta$ 4.26 (dd, *J* = 12.9, 7.6 Hz) and 4.23 (dd, *J* = 12.9, 9.0 Hz)], two saturated and identical fatty acid moieties, and one *E*-crotonoyl moiety [$\delta$ 6.15 (m, 1H), 5.75 (d, *J* = 15.3 Hz, 1H), 1.85 (br d, *J* = 5.5 Hz, 3H)]. The symmetric nature of the spectrum located the crotonoyl residue at C-2, and the HRMS (MW = 692, $C_{43}H_{80}O_6$) was used to identify the fatty acid as stearic acid. To the best of our knowledge, triglycerides bearing very short (<C5) acyl moieties have not been reported before in plants, and **7** adds to the growing list of unusual triglycerides reported from the plant kingdom.[18]

$\alpha$-Bisabolol (**1**) shows an interesting anti-inflammatory activity in vivo,[19] but its mechanism of action is still poorly known, while the fucopyranoside **2a** has been reported to share the same weak cytotoxicity of **1**, but, at least in silico, to show a better brain penetration,[20] an observation interesting for the apoptosis-inducing properties of $\alpha$-bisabolol on glioma cell lines.[10] Keeping in mind the existence of an "$\alpha$-bisabolol issue" in the cosmetic market and the easy availability of **2a**, we have compared the action of $\alpha$-bisabolol (**1**), the fucopyranoside **2a**, and its 3′-senecioyl derivative **2b** against NF-$\kappa$B and STAT-3. These two transcription factors represent veritable master switches of inflammation and are both of great relevance for cosmetic research.[21] The NF-$\kappa$B pathway has been proposed as one of the molecular targets inhibited by $\alpha$-bisabolol in LPS-stimulated RAW264.7 macrophages,[22] but, in the present work, all three compounds showed only a modest action on TNF$\alpha$-mediated NF-$\kappa$B activation. On the other hand, the fucopyranoside **2a**, but not its acyl derivative **2b**, was a good inhibitor of IFN-induced STAT-3 activation and was more potent than $\alpha$-bisabolol, for which the activity in this assay was marginal (Table 1). Non-peptidic STAT-3 inhibitors are generally electrophilic Michael acceptors.[23] This type of reactivity is lacking in bisabolol derivatives, and their mechanism of inhibition might be similar to that of the stilbenoid resveratrol and involve noncovalent reduction of the phosphorylation state of the STAT3 protein.[24] While clearly awaiting mechanistic confirmation and a larger structure−activity study, these observations provide, nevertheless, a strong rationale for using **2a** as a lead structure for medicinal chemistry projects aiming at the

**Table 1. $IC_{50}$ ($\mu$M) Values of $\alpha$-Bisabolol (1) and Its Analogues 2a and 2b toward NF-$\kappa$B and STAT-3 Activation**

| compound | NF-kB | STAT-3 |
|---|---|---|
| $\alpha$-bisabolol (**1**) | >220 | 73 |
| $\alpha$-bisabolol $\beta$-D-fucopyranoside (**2a**) | 110 | 6.3 |
| *O*-3′-senecioyl $\alpha$-bisabolol $\beta$-D-fucopyranoside (**2b**) | 60 | 110 |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development of either anti-inflammatory or apoptosis-inducing agents.[10,20] On a more immediate strategic level, the easy availability of **2a**, its activity on a key factor involved in inflammation and skin carcinogenesis, and its better hydrophilicity and easier formulation in polar solvent combine to qualify it as a potential alternative to natural $\alpha$-bisabolol (**1**) for the cosmetic market.

## ■ EXPERIMENTAL SECTION

**General Experimental Procedures.** Optical rotations ($CHCl_3$) were measured at 589 nm on a JASCO P2000 polarimeter, and IR spectra on a FT-IR Thermo Nicolet apparatus. $^1$H (700 or 300 MHz) and $^{13}$C (175 MHz) NMR spectra of the bisabolane derivatives were measured on a Varian INOVA spectrometer, and the $^1$H NMR spectrum of the triglyceride **7** was measured at 300 MHz (JEOL Eclipse 300). Chemical shifts were referenced to the residual solvent signal ($CDCl_3$: $\delta_H$ = 7.26, $\delta_C$ = 77.0, $CD_3OD$: $\delta_H$ = 3.34, $\delta_C$ = 49.0). Homonuclear $^1$H connectivities were determined by the COSY experiment. One-bond heteronuclear $^1$H−$^{13}$C connectivities were determined with the HSQC experiment. Through-space $^1$H connectivities were evidenced using a ROESY experiment with a mixing time of 250 ms. Two- and three-bond $^1$H−$^{13}$C connectivities were determined by gradient 2D HMBC experiments optimized for a $^{2,3}J$ = 9 Hz. Low- and high-resolution ESIMS were obtained on a LTQ OrbitrapXL (Thermo Scientific) mass spectrometer. Silica gel 60 (70−230 mesh) and RP-18 used for gravity column chromatography were purchased from Macherey-Nagel. Reactions were monitored by TLC on Merck 60 F254 (0.25 mm) plates, which were visualized by UV inspection and/or staining with 5% $H_2SO_4$ in ethanol and heating. Organic phases were dried with $Na_2SO_4$ before evaporation. Flash chromatography was carried out on a Biotage SP-1. HPLC were achieved on a Knauer apparatus equipped with a refractive index detector. The Knauer HPLC apparatus was used to purify all final products. LUNA (normal phase, SI60, 250 × 4 mm) (Phenomenex) columns were used, with 0.7 mL/min as flow rate.

**Plant Material.** *Carthamus glaucus* was collected in the outskirts of Diyarbakir (Turkey) in July 2008 and was identified by Dr. A. Selçuk Ertekin (University of Dicle, Turkey). A voucher specimen (DUF 6978) is kept at Dicle University (Sciences Faculty Herbarium).

**Extraction and Isolation.** Nonwoody dried, powdered flowered aerial parts (400 g) were extracted with acetone (4.4 L × 2). Removal of the solvent left 26.7 g (6.7%) of a black gum, which was purified by solid-phase extraction of RP18 silica gel. For this purpose, the extract was dissolved in a minimum amount of acetone. RP silica gel (75 g) was added next, and the suspension was evaporated. Using a suction filtration funnel, the solid phase was stratified over a RP18 silica gel bed (125 g), and the bed was treated sequentially with MeOH (750 mL) and acetone (900 mL). After removal of the solvent, a 15 g residue from the methanol washing and 5 g from the acetone washing remained. The former was purified by gravity column chromatography on silica gel (125 g, petroleum ether−EtOAc gradient, from 9:1 to 1:9) to afford 122 mg of **6b**, 120 mg **6a**, 8.03 g of **2a** (2%), and 2.1 and 1.7 g of mixtures of less polar and more polar analogues, respectively. The mixtures were repeatedly fractionated by Biotage flash chromatography (petroleum ether−EtOAc mixtures) and next by HPLC on silica gel (methanol−water as mixtures) to eventually afford **2b** (0.048%), **2c** (0.095%), **2d** (0.014%), **2e** (0.047%), **3** (0.28%), **4a** (0.053%), **4b** (0.020%), **5a** (0.018%), and **5b** (0.022%). The acetone washings were fractionated by gravity column chromatography on neutral alumina (75 g, petroleum ether−EtOAc gradient, from 9:1 to 8:2) to afford 150 mg of taraxasterol and 156 mg of the triglyceride **7**.

***O*-3′-Senecioyl $\alpha$-bisabolol $\beta$-D-fucopyranoside (2b):** colorless foam; $[\alpha]_D$ +2.6 (*c* 0.056, $CHCl_3$); $^1$H NMR (700 MHz, $CDCl_3$) $\delta$ 5.81 (1H, br s, H-2″), 5.35 (1H, m, H-2), 5.03 (1H, t, *J* = 6.4 Hz, H-10), 4.89 (1H, dd, *J* = 8.5, 1.2 Hz, H-3′), 4.48 (1H, d, *J* = 6.8 Hz, H-1′), 3.79 (1H, br s, H-4′), 3.77 (1H, dd, *J* = 8.5, 6.8 Hz, H-2′), 3.66 (1H, br q, *J* = 6.2 Hz, H-5′), 2.21 (3H, m, $H_3$-4″), 2.17 (1H, m, H-9a), 1.98 (2H, overlapped, H-3a, H-6a), 1.97 (1H, overlapped, H-9b), 1.95 (2H, overlapped, H-3b, H-6b), 1.94 (3H, m, $H_3$-5″), 1.78 (1H, m, H-1), 1.66 (3H, s, H-12), 1.64 (3H, s, H-15), 1.61 (3H, s, H-13), 1.61 (1H, overlapped, H-8a), 1.48 (1H, ddd, *J* = 13.0, 4.9, 1.5 Hz, H-8b), 1.31 (2H, overlapped, $H_2$-5), 1.27 (3H, d, *J* = 6.2 Hz, H-6′), 1.14 (3H, s, H-14); $^{13}$C NMR ($CDCl_3$, 175 MHz) $\delta$ 171.3 (s, C-1″), 158.2 (s, C-3″), 135.1 (s, C-1), 131.7 (s, C-11), 125.1 (d, C-10), 120.5 (d, C-2), 116.3 (d, C-2″), 97.8 (d, C-1′), 82.3 (s, C-7), 74.6 (d, C-3′), 73.7 (d, C-2′), 71.0 (d, C-4′), 70.4 (d, C-5′), 41.1 (d, C-4), 38.2 (t, C-8), 31.5 (t, C-6), 26.9 (t, C-3), 26.4 (q, C-13), 23.8 (t, C-5), 23.2 (q, C-15), 22.5 (q, C-4″), 21.9 (t, C-9), 20.5 (q, C-14), 19.9 (q, C-5″), 18.9 (q, C-12), 16.7 (q, C-6′); (+) ESIMS *m/z* 473 [M + Na]$^+$; HRESIMS *m/z* 473.2872, calcd for $C_{26}H_{42}NaO_6$, 473.2879.

***O*-3′-Isovaleroyl $\alpha$-bisabolol $\beta$-D-fucopyranoside (2c):** colorless foam; $[\alpha]_D$ +1.2 (*c* 0.10, $CHCl_3$); $^1$H NMR (700 MHz, $CDCl_3$) $\delta$ 5.35 (1H, m, H-2), 5.04 (1H, t, *J* = 6.4 Hz, H-10), 4.88 (1H, dd, *J* = 8.5, 1.2 Hz, H-3′), 4.48 (1H, d, *J* = 6.8 Hz, H-1′), 3.79 (1H, br s, H-4′), 3.77 (1H, dd, *J* = 8.5, 6.8 Hz, H-2′), 3.66 (1H, br q, *J* = 6.2 Hz, H-5′), 2.30 (1H, m, H-3″), 2.17 (1H, overlapped, H-2″a), 2.17 (1H, overlapped, H-9a), 2.12 (1H, overlapped, H-2″b), 1.98 (2H, overlapped, H-3a, H-6a), 1.97 (1H, overlapped, H-9b), 1.95 (2H, overlapped, H-3b, H-6b), 1.78 (1H, m, H-1), 1.66 (3H, s, H-12), 1.64 (3H, s, H-15), 1.61 (3H, s, H-13), 1.61 (1H, overlapped, H-8a), 1.48 (1H, ddd, *J* = 13.0, 4.9, 1.5 Hz, H-8b), 1.31 (2H, overlapped, $H_2$-5), 1.27 (3H, d, *J* = 6.2 Hz, H-6′), 1.14 (3H, s, H-14), 1.00 (6H, d, *J* = 6.5 Hz, $H_3$-4″ and $H_3$-5″); $^{13}$C NMR ($CDCl_3$, 175 MHz) $\delta$ 173.1 (s, C-1″), 135.1 (s, C-1), 131.7 (s, C-11), 125.1 (d, C-10), 120.5 (d, C-2), 97.8 (d, C-1′), 82.3 (s, C-7), 74.9 (d, C-3′), 73.7 (d, C-2′), 71.0 (d, C-4′), 70.4 (d, C-5′), 44.6 (d, C-3″), 41.1 (d, C-4), 38.2 (t, C-8), 31.5 (t, C-6), 26.9 (t, C-3), 26.4 (q, C-13), 26.3 (t, C-2″), 23.8 (t, C-5), 23.2 (q, C-15), 22.5 (q, C-4″ and C-5″), 21.9 (t, C-9), 20.5 (q, C-14), 18.9 (q, C-12), 16.7 (q, C-6′); HRESIMS *m/z* 475.3040, calcd for $C_{26}H_{44}NaO_6$, 475.3036.

***O*-3′-(2,3-Dehydro-$\beta$-methyl)valeroyl-$\alpha$-bisabolol $\beta$-D-fucopyranoside (2d):** colorless foam; $[\alpha]_D$ +6.7 (*c* 0.012, $CHCl_3$); $^1$H NMR (700 MHz, $CDCl_3$) $\delta$ 5.80 (1H, br s, H-2″), 5.38 (1H, m, H-2), 5.03 (1H, t, *J* = 6.4 Hz, H-10), 4.89 (1H, dd, *J* = 8.5, 1.2 Hz, H-3′), 4.46 (1H, d, *J* = 6.8 Hz, H-1′), 3.79 (1H, br s, H-4′), 3.77 (1H, dd, *J* = 8.5, 6.8 Hz, H-2′), 3.66 (1H, br q, *J* = 6.2 Hz, H-5′), 2.20 (3H, m, $H_3$-4″), 2.17 (1H, m, H-9a), 1.98 (2H, overlapped, H-3a, H-6a), 1.97 (1H, overlapped, H-9b), 1.95 (2H, overlapped, H-3b, H-6b), 1.94 (2H, m, $H_2$-5″), 1.78 (1H, m, H-1), 1.66 (3H, s, H-12), 1.64 (3H, s, H-15), 1.61 (3H, s, H-13), 1.61 (1H, overlapped, H-8a), 1.48 (1H, ddd, *J* = 13.0, 4.9, 1.5 Hz, H-8b), 1.31 (2H, overlapped, $H_2$-5), 1.27 (3H, d, *J* = 6.2 Hz, H-6′), 1.14 (3H, s, H-14), 1.10 (3H, t, *J* = 6.9 Hz, $H_3$-6″); $^{13}$C NMR ($CDCl_3$, 175 MHz) $\delta$ 172.0 (s, C-1″), 156.1 (s, C-3″), 135.1 (s, C-1), 131.7 (s, C-11), 125.1 (d, C-10), 120.5 (d, C-2), 114.8 (d, C-2″), 97.8 (d, C-1′), 82.3 (s, C-7), 74.1 (d, C-3′), 73.7 (d, C-2′), 71.0 (d, C-4′), 70.4 (d, C-5′), 41.1 (d, C-4), 38.2 (t, C-8), 31.5 (t, C-6), 26.9 (t, C-3), 26.4 (q, C-13), 24.9 (t, C-5″), 23.8 (t, C-5), 23.2 (q, C-15), 22.0 (q, C-4″), 21.9 (t, C-9), 20.5 (q, C-14), 18.9 (q, C-12), 16.7 (q, C-6′), 12.0 (q, C-6″); (+) ESIMS *m/z* 487 [M + Na]$^+$; HRESIMS *m/z* 487.3031, calcd for $C_{27}H_{44}NaO_6$, 487.3036.

***O*-3′-($\beta$-Methyl)valeroyl $\alpha$-bisabolol $\beta$-D-fucopyranoside (2e):** colorless foam; $[\alpha]_D$ +2.8 (*c* 0.056, $CHCl_3$); $^1$H NMR (700 MHz, $CDCl_3$) $\delta$ 5.35 (1H, m, H-2), 5.03 (1H, t, *J* = 6.4 Hz, H-10), 4.89 (1H, dd, *J* = 8.5, 1.2 Hz, H-3′), 4.48 (1H, d, *J* = 6.8 Hz, H-1′), 3.81 (1H, br s, H-4′), 3.77 (1H, dd, *J* = 8.5, 6.8 Hz, H-2′), 3.66 (1H, br q, *J* = 6.2 Hz, H-5′), 2.41 (1H, dd, *J* = 12.5, 3.2 Hz, H-2″a), 2.21 (1H, dd, *J* = 12.5, 6.5 Hz, H-2″b), 2.18 (1H, m, H-3″), 2.17 (1H, m, H-9a), 1.98 (2H, overlapped, H-3a, H-6a), 1.97 (1H, overlapped, H-9b), 1.95 (2H, overlapped, H-3b, H-6b), 1.78 (1H, m, H-1), 1.66 (3H, s, H-12), 1.64 (3H, s, H-15), 1.61 (3H, s, H-13), 1.61 (1H, overlapped, H-8a), 1.48 (1H, ddd, *J* = 13.0, 4.9, 1.5 Hz, H-8b), 1.31 (2H, overlapped, $H_2$-5), 1.30 (2H, overlapped, H-4″), 1.27 (3H, d, *J* = 6.2 Hz, H-6′), 1.14 (3H, s, H-14), 0.97 (3H, d, *J* = 6.9 Hz, $H_3$-6″), 0.90 (3H, t, *J* = 6.9 Hz, $H_3$-5″); $^{13}$C NMR ($CDCl_3$, 175 MHz) $\delta$ 173.3 (s, C-1″), 135.1 (s, C-1), 131.7 (s, C-11), 125.1 (d, C-10), 120.5 (d, C-2), 97.8 (d, C-1′), 82.3 (s, C-7), 73.9 (d, C-3′), 73.6 (d, C-2′), 71.2 (d, C-4′), 70.3 (d, C-5′), 41.1 (d, C-4), 40.9 (t, C-2″), 38.2 (t, C-8), 31.9 (d, C-3″), 31.5 (t, C-6), 29.8 (t, C-4″), 26.9 (t, C-3), 26.4 (q, C-13), 23.8 (t, C-5), 23.2 (q, C-15), 21.9 (t, C-9), 20.5 (q, C-14), 20.0 (q, C-6″), 18.9 (q, C-12),

16.7 (q, C-6′), 11.9 (q, C-5″); (+) ESIMS $m/z$ 489 [M + Na]$^+$; HRESIMS $m/z$ 489.3201, calcd for $C_{27}H_{46}NaO_6$, 489.3192.

**2,7,10-Trihydroxybisabola-1(15),11-diene 7-β-D-fucopyranoside (4a):** colorless foam; $[\alpha]_D$ −6.7 ($c$ 0.7, MeOH); $^1$H NMR (700 MHz, $CD_3OD$) 4.90 (1H, br s, H-15a), 4.88 (1H, br s, H-12a), 4.79 (1H, br s, H-12b), 4.70 (1H, br s, H-15b), 4.39 (1H, d, $J$ = 6.4 Hz, H-1′), 3.99 (1H, overlapped, H-2), 3.97 (1H, overlapped, H-10), 3.60 (1H, overlapped, H-5′), 3.59 (1H, overlapped, H-3′), 3.45 (1H, overlapped, H-2′), 3.45 (1H, overlapped, H-4′), 2.39 (1H, m, H-5a), 2.13 (1H, m, H-3a), 2.03 (2H, m, $H_2$-6), 1.97 (1H, m, H-5b), 1.83 (1H, m, H-4), 1.74 (1H, overlapped, H-9a), 1.73 (3H, s, $H_3$-13), 1.63 (1H, overlapped, H-8a), 1.62 (1H, overlapped, H-9b), 1.25 (3H, d, $J$ = 6.9 Hz, $H_3$-6′), 1.16 (3H, s, $H_3$-14), 1.07 (1H, dd, $J$ = 12.9, 8.9 Hz, H-3b); $^{13}$C NMR ($CD_3OD$, 175 MHz) δ 150.0 (s, C-1), 146.3 (s, C-11), 110.1 (t, C-12), 102.8 (t, C-15), 97.3 (d, C-1′), 78.2 (s, C-7), 76.0 (d, C-10), 73.9 (d, C-2′), 71.7 (d, C-3′), 71.6 (d, C-2), 71.2 (d, C-4′), 70.0 (d, C-5′), 44.2 (d, C-4), 37.4 (t, C-3), 33.4 (t, C-5), 27.9 (t, C-6), 27.8 (t, C-9), 19.7 (q, C-14), 16.4 (q, C-13), 15.7 (q, C-6′); (+) ESIMS $m/z$ 423 [M + Na]$^+$; HRESIMS $m/z$ 423.2364, calcd for $C_{21}H_{36}NaO_7$, 423.2359.

**2,7,11-Trihydroxybisabola-1(15),9-diene 7-β-D-fucopyranoside (4b):** colorless foam; $[\alpha]_D$ −15.0 ($c$ 0.02, MeOH); $^1$H NMR (700 MHz, $CD_3OD$) δ 5.83 (1H, dt, $J$ = 15.1, 6.9, 6.9 Hz, H-9), 5.64 (1H, d, $J$ = 15.1 Hz, H-10), 4.91 (1H, br s, H-15a), 4.71 (1H, br s, H-15b), 4.44 (1H, d, $J$ = 6.4 Hz, H-1′), 3.95 (1H, m, H-2), 3.60 (1H, overlapped, H-5′), 3.59 (1H, overlapped, H-3′), 3.46 (1H, overlapped, H-2′), 3.45 (1H, overlapped, H-4′), 2.42 (1H, overlapped, H-8a), 2.41 (1H, overlapped, H-5a), 2.29 (1H, dd, $J$ = 12.1, 6.9 Hz, H-8b), 2.15 (1H, m, H-3a), 2.03 (2H, overlapped, $H_2$-6), 2.00 (1H, overlapped, H-5b), 1.92 (1H, m, H-4), 1.28 (6H, s, $H_3$-12 and $H_3$-13), 1.25 (3H, d, $J$ = 5.9 Hz, $H_3$-6′), 1.18 (3H, s, $H_3$-14), 1.13 (1H, m, H-3b); $^{13}$C NMR ($CD_3OD$, 175 MHz) δ 150.0 (s, C-1), 137.5 (d, C-10), 127.8 (d, C-9),102.8 (t, C-15), 97.2 (d, C-1′), 78.2 (s, C-7), 73.9 (d, C-2′), 71.7 (d, C-3′), 71.6 (d, C-2), 71.2 (d, C-4′), 70.8 (s, C-11), 70.0 (d, C-5′), 44.2 (d, C-4), 37.4 (t, C-3), 33.4 (t, C-5), 31.0 (q, C-12 and C-13), 27.9 (t, C-6), 19.7 (q, C-14), 16.4 (q, C-13), 15.7 (q, C-6′); (+) ESIMS $m/z$ 423 [M + Na]$^+$; HRESIMS $m/z$ 423.2351, calcd for $C_{21}H_{36}NaO_7$, 423.2359.

**1-Hydroperoxy-7,10-dihydroxybisabola-2,11-diene 7-β-D-fucopyranoside (5a):** colorless foam; $[\alpha]_D$ −11.0 ($c$ 0.05, MeOH); $^1$H NMR (700 MHz, $CD_3OD$) δ 6.19 (1H, dd, $J$ = 10.4, 2.1 Hz, H-3), 5.56 (1H, d, $J$ = 10.4 Hz, H-2), 4.97 (1H, br s, H-12a), 4.75 (1H, br s, H-12b), 4.43 (1H, d, $J$ = 6.1 Hz, H-1′), 3.96 (1H, m, H-10), 3.62 (1H, overlapped, H-5′), 3.61 (1H, overlapped, H-3′), 3.48 (1H, overlapped, H-2′), 3.46 (1H, overlapped, H-4′), 2.40 (1H, m, H-1), 2.20 (1H, dd, $J$ = 12.2, 2.5 Hz, H-5a), 1.75 (2H, overlapped, $H_2$-6), 1.73 (3H, br s, $H_3$-13), 1.70 (1H, overlapped, H-8a), 1.69 (1H, overlapped, H-9a), 1.65 (1H, overlapped, H-5b), 1.63 (1H, overlapped, H-9b), 1.51 (1H, overlapped, H-8b), 1.29 (3H, s, H-15), 1.27 (3H, d, $J$ = 6.2 Hz, H-6′), 1.21 (3H, s, H-14); $^{13}$C NMR ($CD_3OD$, 175 MHz) δ 148.6 (s, C-11), 134.0 (d, C-2), 129.8 (d, C-3), 109.8 (d, C-12), 97.5 (d, C-1′), 80.7 (s, C-7), 78.7 (s, C-1), 76.2 (d, C-10), 74.2 (d, C-2′), 72.0 (d, C-3′), 71.6 (d, C-4′), 70.4 (d, C-5′), 44.2 (d, C-4), 37.4 (t, C-8), 31.7 (t, C-5), 26.7 (t, C-9), 23.6 (q, C-14), 22.2 (q, C-15), 19.3 (t, C-6), 17.0 (q, C-13), 15.9 (q, C-6′); (+) ESIMS $m/z$ 439 [M + Na]$^+$; (+) ESIMS $m/z$ 439 [M + Na]$^+$; HRESIMS $m/z$ 439.2312, calcd for $C_{21}H_{36}NaO_8$, 439.2308.

**1-Hydroperoxy-7,12-dihydroxybisabola-2,10-diene 7-β-D-fucopyranoside (5b):** colorless foam; $[\alpha]_D$ −4.8 ($c$ 0.02, $CHCl_3$); $^1$H NMR (700 MHz, $CD_3OD$) δ 6.18 (1H, dd, $J$ = 10.0, 2.1 Hz, H-3), 5.53 (1H, d, $J$ = 10.0 Hz, H-2), 5.23 (1H, t, $J$ = 5.6 Hz, H-10), 4.42 (1H, d, $J$ = 6.1 Hz, H-1′), 4.10 (1H, d, $J$ = 12.5 Hz, H-12a), 4.05 (1H, d, $J$ = 12.5 Hz, H-12b), 3.59 (1H, overlapped, H-5′), 3.58 (1H, overlapped, H-3′), 3.44 (1H, overlapped, H-2′), 3.44 (1H, overlapped, H-4′), 2.38 (1H, m, H-4), 2.20 (1H, overlapped, H-6a), 2.19 (1H, overlapped, H-9a), 2.14 (1H, overlapped, H-9b), 1.83 (1H, m, H-8a), 1.74 (3H, br s, $H_3$-13), 1.65 (1H, overlapped, H-5a), 1.62 (1H, overlapped, H-5b), 1.53 (1H, m, H-8b), 1.33 (1H, m, H-6b), 1.26 (3H, s, H-15), 1.22 (3H, d, $J$ = 6.2 Hz, $H_3$-6′), 1.22 (3H, s, $H_3$-14); $^{13}$C NMR ($CD_3OD$, 175 MHz) δ 134.1 (d, C-2), 133.8 (s, C-11), 129.2 (d, C-3), 128.0 (d, C-10), 97.2 (d, C-1′), 80.5 (s, C-7), 77.9 (s, C-1), 73.9 (d, C-2′), 71.7 (d, C-3′), 71.2 (d, C-4′), 70.1 (d, C-5′), 60.0 (t, C-12), 37.1 (t, C-8), 31.7 (t, C-6), 28.4 (q, C-15), 21.2 (t, C-9), 20.5 (q, C-14), 20.2 (q, C-13), 20.0 (t, C-5), 15.7 (q, C-6′); (+) ESIMS $m/z$ 439 [M + Na]$^+$; HRESIMS $m/z$ 439.2313, calcd for $C_{21}H_{36}NaO_8$, 439.2308.

**2-Crotonoyl-1,3-distearoylglycerol (7):** colorless foam; IR (KBr disk) 3010, 1745, 1690, 1340, 1269, 1245, 1135, 1015 cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$) δ 6.15 (1H, m), 5.75 (1H, d, $J$ = 15.3 Hz), 5.32 (1H, m), 4.26 (2H, dd, $J$ = 12.9, 7.6 Hz), 4.23 (2H, dd, $J$ = 12.9, 9.0 Hz), 2.30 (4H, t, $J$ = 6.8 Hz), 1.85 (3H, br d, $J$ = 5.5 Hz), 1.56 (4H, br t, $J$ = 6.8 Hz), 1.24 (56 H, br s), 0.87 (3H, t, $J$ = 6.7 Hz); HRESIMS $m/z$ 715.5842, calcd for $C_{43}H_{80}NaO_6$, 715.5853.

**Biological Assays.** To determine NF-κB-dependent transcription of HIV-1-LTR-luc, 5.1 cells were preincubated for 30 min with the compounds tested as indicated, followed by stimulation with TNFα (2 ng/mL) for 6 h. Then, cells were lysed in 25 mM Tris-phosphate pH 7.8, 8 mM $MgCl_2$, 1 mM DTT, 1% Triton X-100, and 7% glycerol. Luciferase activity was measured using an Autolumat LB 9510 (EG&G Berthold, Oak Ridge, TN, USA) following the instructions of the luciferase assay kit (Promega, Madison, WI, USA), and protein concentration was measured by the Bradford method. The background obtained with the lysis buffer was subtracted from each experimental value, the RLU/μg of protein was calculated, and the specific transactivation was expressed as the percentage of transcriptional activity compared to TNF-α alone (100%). All experiments were repeated at least four times.

To determine STAT-3 transcriptional activity, HeLa cells were transiently transfected with the plasmid p4xM67-tk-Luc, in which the luciferase gene is driven by a promoter containing four copies of the STAT-binding site. Twenty-four hours after transfection, the cells were incubated with the test compounds for 30 min and then stimulated with IFNγ (10 u/mL) for 6 h, measuring the luciferase activity as described above. Basal luciferase activity was subtracted from IFNγ-induced activity to calculate 100% of activation. The inhibitory activity of the compounds is the percentage of induction compared to IFNγ and $IC_{50}$ activity and was calculated using a SigmaPlot software.

## ■ ASSOCIATED CONTENT

### Ⓢ Supporting Information

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### Notes

The authors declare no competing financial interest.

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## ■ DEDICATION

Dedicated to Dr. Gordon M. Cragg, formerly Chief, Natural Products Branch, National Cancer Institute, Frederick, Maryland, for his pioneering work on the development of natural product anticancer agents.

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