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Ring B functionalization of scalarane sesterterpenes by radical relay halogenation

Veaceslav Kulciţki,*,† Nicon Ungur,† Margherita Gavagnin, Francesco Castelluccio and Guido Cimino

Istituto di Chimica Biomolecolare, CNR, Via Campi Flegrei 34, I-80078 Pozzuoli (Na), Italy

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Abstract—The functionalization of the B-ring of the scalarane framework has been achieved for the first time by a radical relay halogenation (RRH) synthetic method. The known scalaranic methyl ester, which was prepared by a procedure with an overall yield higher than those reported in the literature, has been used as the starting substrate. Some theoretical considerations explaining the course of RRH reaction are also presented.

1. Introduction

The scalarane compounds, the first member of which was scalaradial (**1**),[1] are a very interesting group of natural products typically isolated from both marine sponges and molluscs (Fig. 1).[2] These molecules show diverse pharmacological properties including cytotoxicity, antimicrobial and anti-inflammatory activity, platelet aggregation inhibition.[3] An involvement of these sesterterpenoids in the defensive mechanisms of sponges and molluscs has also been demonstrated.[4] The structural diversity in the scalarane family mainly arises from the different arrangement of the oxidized carbons C-19 and C-20, which can be involved in a cyclization process to form a five-membered ring with higher or lower oxidation [i.e., scalarin (**2**)[5]]. The majority of natural scalaranes are characterized by the presence of an oxygenated functional group at C-12, such as scalaradial (**1**) and related compounds. However, a number of natural scalaranes display additional oxygenated groups at different positions of the tetracyclic framework [i.e., heteronemin (**3**),[6] 3-keto-deoxoscalarin (**4**),[7] 6-keto-deoxoscalarin (**5**)[8]]. The B-ring functionalization has also been reported for a series of scalaranes (i.e., **6**) isolated from ferns, the only report of scalarane occurrence in plants.[9]

Although different synthetic pathways toward this class of compounds have been elaborated,[10] previous work on the synthesis of scalarane derivatives was focused mainly on compounds displaying functional groups in the D-ring. We report here our study toward the functionalization at ring B by using a radical relay halogenation (RRH) method. This investigation resulted in the synthesis of scalarane compounds functionalized at the C-6 and C-7 positions.

2. Results and discussion

The synthetic strategy was based on assembling the scalarane skeleton, followed by a remote functionalization procedure. The most convenient synthetic methodology leading to the scalarane structure includes a C_5 homologation of the readily available manool (**7**), followed by a superacid-induced cyclization[11] that provides scalaranic ester (**10**) (Scheme 1).

However, this sequence of transformations contains two difficult separation steps involving silver nitrate impregnated silica gel column chromatography for the isolation of the *E*-ketone **8** and *E*-ester **9**. Taking into consideration the fact that the formation of the scalaranic framework is not influenced by the configuration of the Δ^{13}-double bond,[12] we decided to simplify the methodology starting from the commercially available labdanic compound, sclareol (**11**) (Scheme 2).

The C_3 homologation of **11** was achieved according to the methodology described previously.[13] Treatment of **11** with ethylacetoacetate provided the mixture of ketones **12**. The Horner olefination of ketones **12** gave the mixture of esters

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* Corresponding author. Fax: +39 373 22 739954; e-mail: kulcitki@yahoo.com
† On leave from Institute of Chemistry, Moldova Academy of Sciences, str. Academiei 3, MD-2028 Chişinău, Republic of Moldova.

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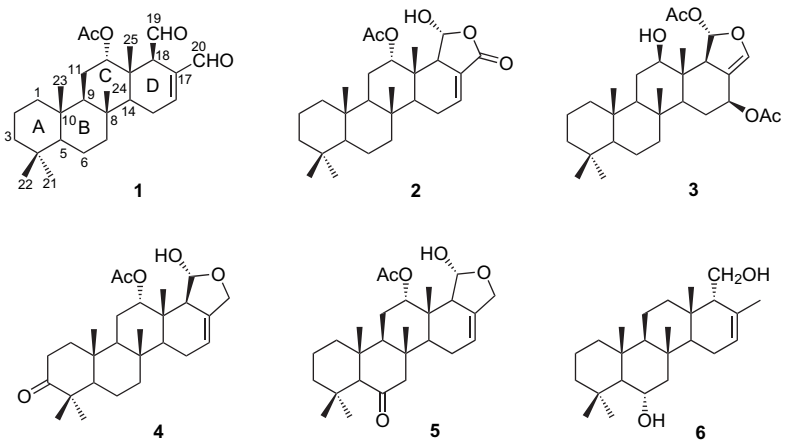
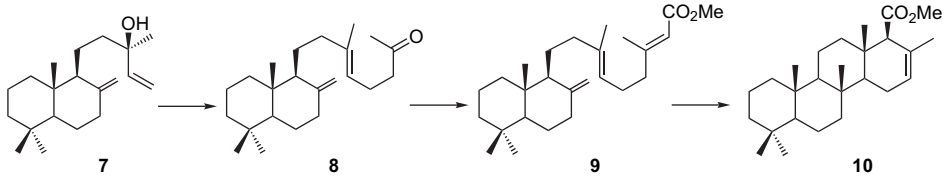
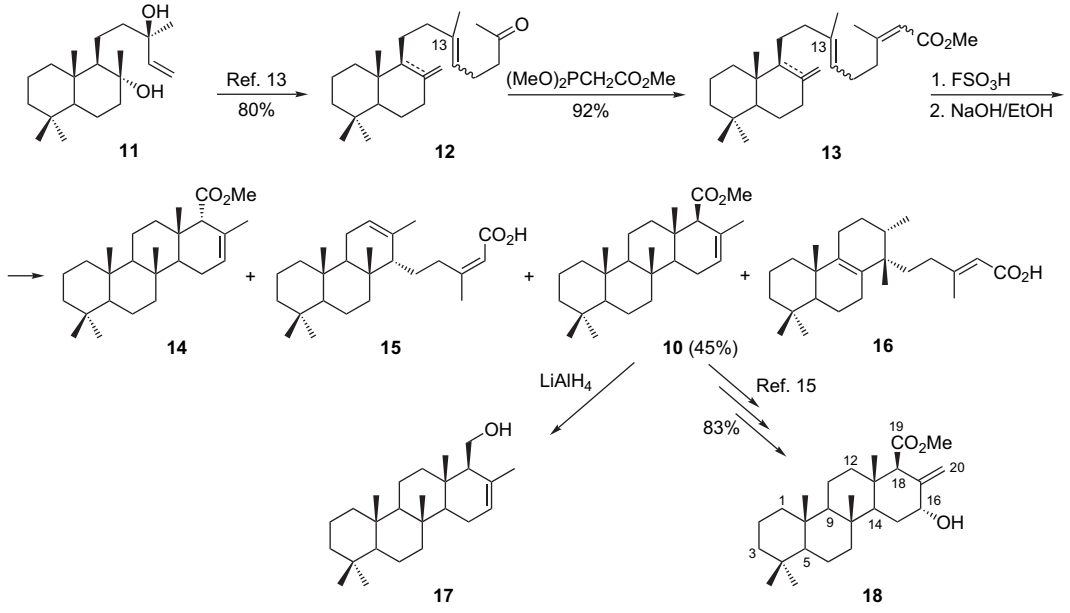


Figure 1. Representative members of scalarane family.



Scheme 1. Synthesis of methyl 18α*H*-scalar-16-en-19-oate (**10**) from manool (**7**).[11]



Scheme 2. Synthesis of methyl 18α*H*-scalar-16-en-19-oate (**10**) and methyl 18α*H*-scalar-16α-ol-17(20)-en-19-oate (**18**) from sclareol (**11**).

13. Superacid cyclization of this mixture, followed by alkaline hydrolysis, provided the desired scalarane esters **10** and **14**, which were formed along with cheilanthane and rearranged cheilanthane acids **15** and **16**. Flash chromatography of this mixture on Si gel provided scalaranic ester **10** in an overall yield of 33% after four steps. To the best of our knowledge, this is the highest overall yield of a scalarane compound starting from a commercial product.[10]

The subsequent transformation of the ester **10** into a B-ring oxidized scalarane was planned to be performed by the remote functionalization strategy, which has been broadly used in the field of isoprenoids.[14] The characteristic feature of these reactions is the generation of a free radical in the molecule of the substrate, that has to contain a suitable functional group playing the role of a 'relay' for the free radical formation, followed by the functionalization of nearby disposed C–H bond by this radical. The position of functionalization is governed mostly by steric factors. The ester group of **10** can be reduced to the alcohol functionality as a radical relay handle but, for the B-cycle functionalization of scalaranic skeleton, the hydroxyl group in the corresponding

alcohol **17** is disposed too far and cannot interact specifically with the corresponding C–H bonds due to the steric hindrance of the angular methyl groups.

Therefore, we decided to start from another substrate, the alcohol **18**, obtained in two steps from ester **10**,[15] and to apply a well known remote functionalization procedure, the radical relay halogenation (RRH), which was introduced by Breslow and co-workers[16] and used in the field of steroids. This procedure is based on the interaction of the hydroxyl in the substratum with an aromatic acid, containing the iodine atom in the ring, followed by a photolytic halogenation of the resulting ester under the action of a chlorinating agent. As the result, the iodo-aromatic fragment forms a radical that abstracts the hydrogen atom from a tertiary carbon suitably disposed in the spatial surrounding of the molecule to provide a chloro-derivative. The abstraction position is dependent upon geometrical factors. The hydroxyl group at C-16 in compound **18** was recognized as an excellent link for a RRH reaction. In fact, it possesses the α-configuration, which exactly matches the configuration of the tertiary hydrogen atoms H-5 and H-9 in the cycle B. The abstraction of H-5 should lead to a functionalization in the ring B, whereas the abstraction of H-9 should result in obtaining a functional group at ring C. Besides, after introduction of the additional functionality by RRH, the hydroxyl and the ester groups in cycle D could be manipulated easily to provide the dialdehyde fragment of scalaradial **1**[15] or other naturally occurring scalaranes.

According to the conclusions made by Breslow,[16,17] the substitution of a tertiary hydrogen for a chlorine atom depends mainly on geometrical factors. First of all, in order to achieve the transition state, there should be a match between the distance from the hydroxyl oxygen of the substrate to the tertiary hydrogen to be abstracted and the distance from the same hydroxyl oxygen to the chlorine linked to the aromatic fragment.

Molecular modeling simulations showed that, from this point of view, both 3-iodobenzoic and 3-phenylacetic acids meet these requirements for the abstraction of the hydrogen at either the C-9 or C-5 position of the scalaranic skeleton. The calculated distances in compound **18** from the oxygen atom at C-16 to the hydrogen atom at both C-5 and C-9 are 5.93 and 4.89 Å, respectively. Consequently, 3-iodobenzoic acid (the distance O–Cl in the transition state[16] is 4.3 Å) is a template matching better selection criteria for C-9 abstraction, while 3-iodophenylacetic acid (the distance O–Cl in the transition state[16] is 6.8 Å) is more prone to abstract the hydrogen from C-5 position of the scalarane substrate. The optimized conformations for the aromatic ester derivatives **19** and **20** are shown in Figure 2.

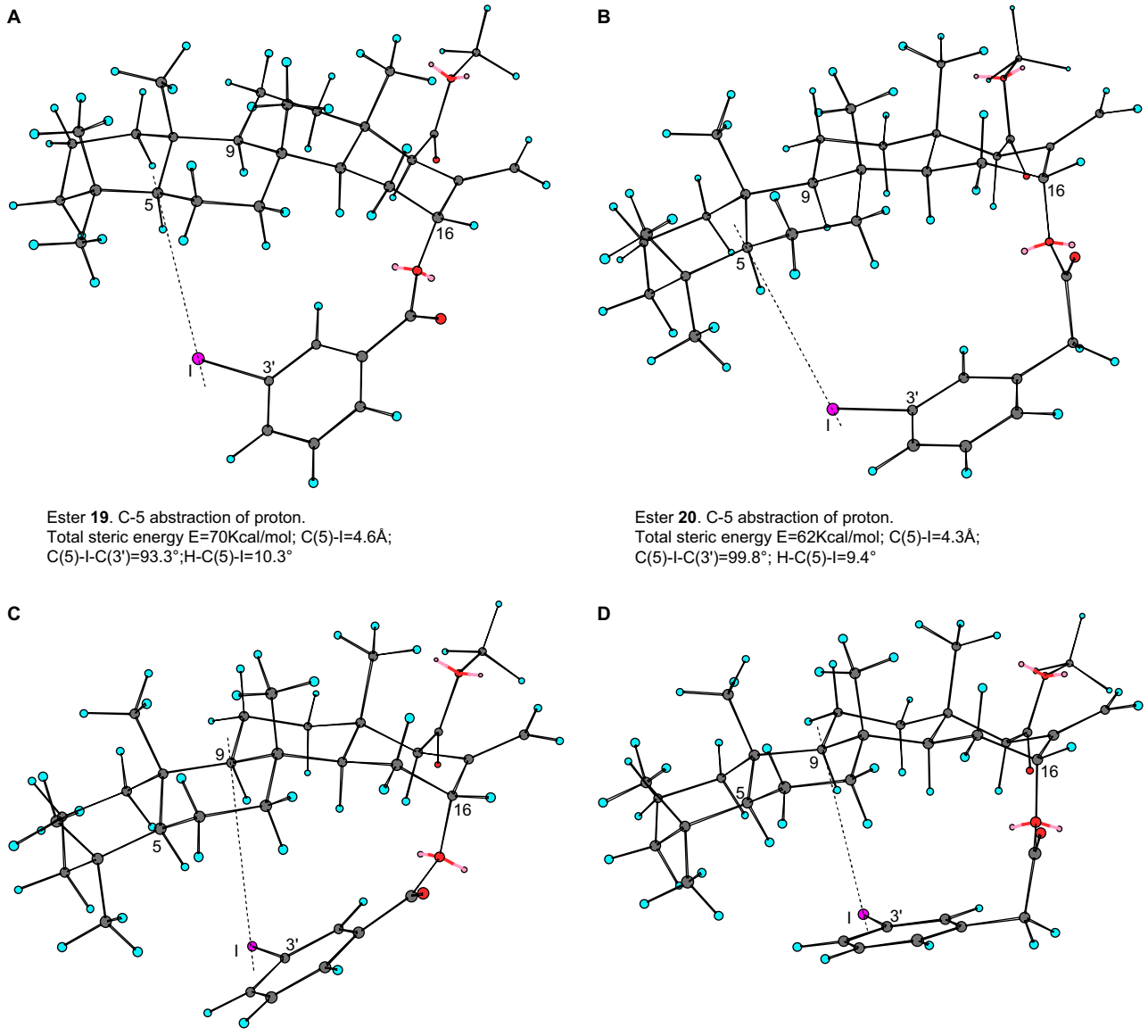
The minimal total repulsion energy for all conformations does not differ significantly, so the probability factor to achieve C-5 or C-9 abstraction of hydrogen atoms is almost equal. But according to Breslow,[17] another requirement for the RRH process is the possibility of obtaining a linear transition state C–H–Cl–I with a total iodine–carbon separation $\leq$5.37 Å. Analysis of molecular modeling calculation data showed that for both esters **19** and **20**, it is not possible to adopt a linear arrangement of the C(9)–H–Cl–I atoms, thus preventing the abstraction of H-9. So, by these considerations, the RRH reaction on both substrates **19** and **20** should only result in the abstraction of the hydrogen atom at C-5. Optimized conformations **A** and **B** of **19** and **20** showed the C(3′)–I–C(5) angle values of 93.3° and 99.8°, respectively, that is close to the linear C(5)–H–Cl–I arrangement, provided the C–I–Cl angle equals 90° in the transition state.[17] For all conformations a slight deviation of the abstraction protons from the C–I axis was observed (see Fig. 2 legends).

These theoretical observations were proven by RRH experiments performed with both compounds **19** and **20**, which only gave product **21**. The synthetic sequence leading to B-cycle functionalized scalarane **23** is shown in Scheme 3.

Esterification of the secondary hydroxyl group in compound **18** proceeded smoothly with acyl chlorides of both 3-iodobenzoic acid and 3-iodophenylacetic acid. The acyl chlorides were obtained from the corresponding acids on treatment with an excess of thionylchloride at reflux.[18] The esterification proceeded in benzene at reflux in the presence of pyridine. Catalytic DMF added to the reaction mixture accelerated the reaction rate. In the case of the less reactive 3-iodobenzoylchloride a threefold excess of chloranhydride assured almost a quantitative yield of the ester **19**.

RRH reactions were performed using different chlorine radical donors and solvent mixtures. In the case of 3-iodobenzyl ester **19** better yields were obtained using iodophenyldichloride[19] in a mixture of dichloromethane/*tert*-butanol, 2:1, under irradiation with two incandescent lamps (100 W+200 W) for 2 h at room temperature. The subsequent dehydrohalogenation–hydrolysis with KOH in a dioxan/methanol mixture provided ester **21**. 3-Iodophenylacetic ester **20** was transformed into the same product **21** under the action of sulfuryl chloride and dibenzoylperoxide in carbon tetrachloride at reflux for 5 h, followed by the same dehydrohalogenation–hydrolysis procedure.

The structure of compound **21** was determined by high resolution mass spectrometry and a detailed 2D-NMR analysis. First of all, the molecular formula $C_{26}H_{40}O_3$, deduced by the sodiated ion peak at *m/z* 423 (M+Na) in the HRESIMS spectrum, exhibited the expected additional unsaturation degree with respect to the starting product **18**. Analysis of ^1H and ^{13}C NMR spectra of **21** in comparison with those of **18**[15,20] showed that the difference was in the presence of a trisubstituted double bond [δ_C 148.1 (s) and 116.4 (d); δ_H 5.39 (m)] in the scalarane skeleton of **21**. The ^1H–^1H COSY spectrum indicated that the olefinic proton at δ 5.39 (H-6) was correlated to a methylene (H_2-7) resonating at δ 1.77 (m) and 1.99 (dd, J=17.5) linked to a quaternary carbon, according to the position of the double bond either at C-5/C-6 or at C-9/C-11. The expected location in the ring B was supported by the down-field shifted ^{13}C values of both β-methyl groups C-21 (δ 29.4 in **21**, δ 21.3 in **18**) and C-23 (δ 20.3 in **21**, δ 16.2 in **18**) of the scalarane framework, due to the different steric arrangement of ring B and absence of the γ-*gauche* effect of C-6. All proton and carbon resonances, assigned by 2D-NMR (^1H–^1H COSY, HMQC, and HMBC) experiments as reported in Section 4, were in agreement with the proposed structure **21**.



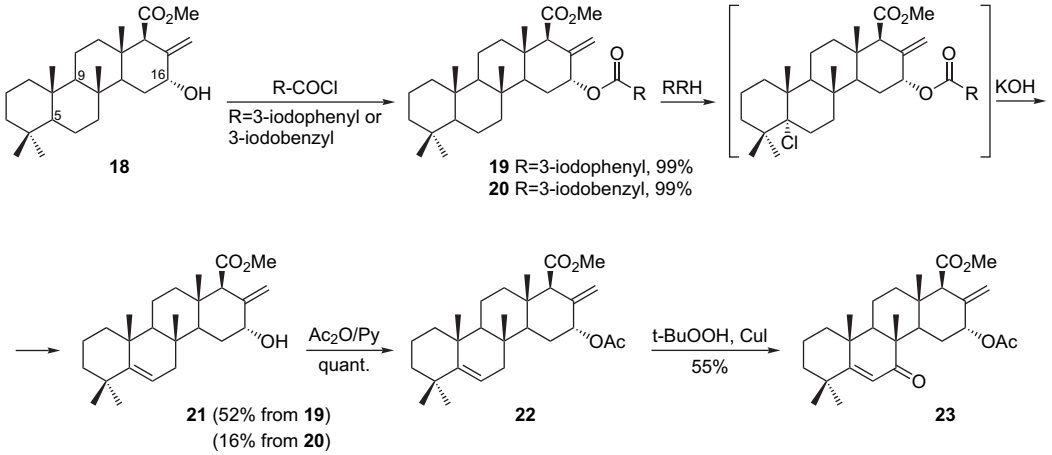
Ester **19**. C-5 abstraction of proton.
Total steric energy E=70Kcal/mol; C(5)-I=4.6Å;
C(5)-I-C(3')=93.3°;H-C(5)-I=10.3°

Ester **20**. C-5 abstraction of proton.
Total steric energy E=62Kcal/mol; C(5)-I=4.3Å;
C(5)-I-C(3')=99.8°; H-C(5)-I=9.4°

Ester **19**. C-9 abstraction of proton.
Total steric energy E=71Kcal/mol; C(9)-I=4.9Å;
C(9)-I-C(3')=65.9°; H-C(9)-I=13.6°

Ester **20**. C-9 abstraction of proton.
Total steric energy E=60Kcal/mol; C(9)-I=4.4Å;
C(9)-I-C(3')=72.4°; H-C(9)-I=13.0°

Figure 2. Optimized conformations of esters **19** and **20**.



Scheme 3. Ring B functionalization of methyl 18α*H*-scalar-16α-ol-17(20)-en-19-oate (**18**) by radical relay halogenation.

Once its structure was proved, ester **21** was subsequently used to functionalize the ring B of the scalaranic framework. Accordingly, acetylation of **21** under standard conditions (Ac_2O–Py) provided the acetate **22** in quantitative yield. The subsequent allylic oxidation of **22** was achieved in an acceptable 55% yield using *tert*-butylhydroperoxide–copper iodide procedure[21] to provide the α,β-unsaturated ketone **23**—a versatile substrate for further transformations.

3. Conclusions

The ring B functionalization of a sesterterpene scalarane has been achieved by using a short and straightforward remote functionalization procedure. The radical relay halogenation method has been used here for the first time on terpenes. The starting oxidized scalarane **18** has been obtained from ester **10**, which has been prepared by an improved procedure in four synthetic steps from commercially available sclareol **11**. The yield of **10** after four steps reached 33% and this is the most efficient scalarane synthesis with respect to the literature.[10] Finally, functionalized scalaranes **21**–**23** could be further transformed to be used for structure–activity relationship studies. These subjects are now under consideration in our laboratories.

4. Experimental

4.1. General procedures

Melting points were measured on a Kofler apparatus. The IR spectra were taken on a Bio-Rad FTS 7 spectrophotometer. NMR experiments were recorded at ICB-NMR Service. 1D- and 2D-NMR spectra were acquired in $CDCl_3$ (δ values are reported and referred to C*H*Cl_3 at 7.26 ppm) on a Bruker Avance-400 operating at 400 MHz, using an inverse probe fitted with a gradient along the *Z*-axis. ^{13}C NMR were recorded on a Bruker DPX-300 operating at 75.5 MHz (δ values are reported to *C*DCl_3, 77.0 ppm) using a dual probe. Optical rotations were measured in $CHCl_3$ on a Jasco DIP 370 polarimeter, using a 10-cm cell. Low and high resolution ESIMS were performed on a Micromass Q-TOF Micro™ coupled with a HPLC Waters Alliance 2695. The instrument was calibrated by using a PEG mixture from 200 to 1000 MW (resolution specification 5000 FWHM, deviation <5 ppm rms in the presence of a known lock mass. Commercial Merck Si gel 60 (70–230 mesh ASTM) was used for column chromatography and Merck precoated Si gel plates were used for TLC. The chromatograms were sprayed with 0.1% $Ce(SO_4)_2$ in 2 N H_2SO_4 and heated at 80 °C for 5 min to detect the spots. The work-up of the reaction mixtures in organic solvents included exhaustive extraction with diethyl ether and washing with water up to neutral reaction, drying over anhydrous Na_2SO_4, filtration, and removal of the solvent in vacuo. For molecular modeling simulations the Chem3D soft was used (CS Chem3D Pro® ©1999 CambridgeSoft Corporation).

4.2. Synthesis of the scalaranic ester 18 from sclareol (11)

4.2.1. Horner olefination of the mixture of ketones 12. The mixture of ketones **12** (4.3 g, 13.03 mmol), obtained from 5 g (16.23 mmol) of sclareol (**11**) according to the described methodology,[13] was dissolved in 230 mL of dry benzene, trimethylphosphonoacetate (6.33 mL, 39.13 mmol) was added, followed by a solution of NaOMe obtained from 0.9 g (39.13 mmol) of sodium dissolved in 23 mL of methanol. The reaction mixture was refluxed under nitrogen for 2 h. Usual work-up provided, after Si gel flash chromatography, 4.628 g (11.99 mmol) of the mixture of esters **13**, which were identified by TLC and ^1H NMR comparison with an authentic sample of pure *E*-isomer **9**.

4.2.2. Superacidic cyclization of the mixture of esters 13. The mixture of esters **13** (3.978 g, 10.31 mmol) was dissolved in dichloromethane (35 mL) and kept at −78 °C. To this cooled solution, a solution of 2.96 mL (51.53 mmol) of fluorosulfonic acid in 10 mL of 2-nitropropane, chilled at the same temperature, was added dropwise. The reaction mixture was stirred at −78 °C for 25 min, then quenched with a solution of triethylamine (16 mL, 155 mmol) in hexane (16 mL). Usual work-up gave the crude reaction product, which was hydrolysed by refluxing for 2 h with a solution of 2.07 g NaOH (51.81 mmol) in 20 mL ethanol. Usual work-up gave the crude product, which was submitted to flash chromatography on Si gel. Elution with 3% EtOAc in petroleum ether gave 1.8 g (4.66 mmol) of pure ester **10**, which was identified by TLC comparison with an authentic sample.

4.2.3. Synthesis of alcohol 18. Alcohol **18** was obtained according to the described methodology[15] involving epoxidation of ester **10**, followed by Al(O*i*-Pr)$_3$-mediated epoxide opening.

4.3. Ring B functionalization of the scalaranic skeleton

4.3.1. Synthesis of 3-iodophenyl ester 19. 3-Iodobenzoic acid (167 mg, 0.672 mmol) was treated with 1.5 mL $SOCl_2$ under reflux for 1 h. Cooling to room temperature was followed by addition of three drops of DMF and refluxing continued for further 30 min. Evaporation of the excess $SOCl_2$ under reduced pressure provided the crude acyl chloride, to which 90 mg of alcohol **18** (0.224 mmol) was added, dissolved in 3 mL of benzene and 0.5 mL of pyridine. After 4 h of reflux, TLC showed no starting material. Usual work-up provided the crude reaction product, which was submitted to Si gel flash chromatography. Elution with 2% EtOAc in petroleum ether provided 140 mg (0.222 mmol, 99%) of ester **19**. Colorless viscous liquid; $[\alpha]_D^{25}$ −32.4 (*c* 0.36, $CHCl_3$); IR ν_{max} (liquid film) 1732, 1716 cm^{-1}. ^1H NMR (400 MHz) δ_H: 8.37 (1H, s, H-2′); 7.99 (1H, d, *J*=7.8 Hz, H-6′); 7.91 (1H, d, *J*=7.9 Hz, H-4′); 7.23 (1H, dd, *J*=7.8 and 7.9 Hz, H-5′); 5.66 (1H, m, H-16); 5.29 (1H, br s, H-20a); 5.09 (1H, br s, H-20b); 3.65 (3H, s, –OMe); 3.21 (1H, s, H-18); 1.99 (1H, m, H-15a); 1.77 (1H, m, H-15b); 1.70 (2H, m, H-1a and H-7a); 1.65 (1H, m, H-2a); 1.60 (2H, m, H-6a and H-12a); 1.53 (1H, m, H-14); 1.50 (2H, m, H_2-11); 1.45 (1H, m, H-12b); 1.40 (2H, m, H-2b and H-6b); 1.35 (1H, m, H-3a); 1.12 (1H, ddd, *J*=13.3, 13.4, and 4.0 Hz, H-3b); 1.07 (3H, s, H_3-25); 0.90 (1H, br d, *J*=10.6 Hz, H-9); 0.86 (3H, s, H_3-24); 0.82 (6H, s, H_3-21 and H_3-23); 0.81 (2H, m, H-5 and H-1b); 0.79 (3H, s, H_3-22). ^{13}C NMR (75.5 MHz) δ_C: 171.4 (C-19); 163.6 (CO–phenyl); 141.7 (C-4′); 139.8 (C-17); 138.6 (C-2′); 132.7

(C-1′); 130.1 (C-5′); 128.7 (C-6′); 115.1 (C-20); 93.8 (C-3′); 76.2 (C-16); 61.2 (C-9); 58.8 (C-18); 56.5 (C-5); 53.7 (C-14); 51.0 (–OMe); 42.1 (C-3); 41.8 (C-7); 40.3 (C-12); 39.8 (C-1); 39.6 (C-13); 37.7 (C-8); 37.6 (C-10); 33.3 (2C, C-4 and C-21); 27.4 (C-15); 21.3 (C-22); 18.6 (C-2); 18.1 (C-6); 17.5 (C-11); 17.1 (C-24); 16.3 (C-23); 14.2 (C-25). HRESIMS: *m/z* $(M+Na)^+$ 655.2276 (655.2260 calcd for $C_{33}H_{45}O_4INa$).

4.3.2. Synthesis of 3-iodobenzyl ester 20. 3-Iodophenylacetic acid (149 mg, 0.567 mmol) was treated with $SOCl_2$ (2 mL) under reflux for 1 h. Cooling to the room temperature was followed by addition of three drops of DMF and refluxing continued for 30 min. Evaporation of the excess $SOCl_2$ under reduced pressure provided the crude acyl chloride, to which 114 mg of alcohol **18** (0.284 mmol) was added, dissolved in 4 mL of benzene and 0.4 mL of pyridine. After 4 h of reflux, TLC showed no starting material. Usual work-up provided the crude reaction product, submitted to flash chromatography on Si gel. Elution with 3% EtOAc in petroleum ether provided 181 mg (0.28 mmol, 99%) of ester **20**. Colorless viscous liquid; $[\alpha]_D^{25}$ −22.6 (*c* 0.12, $CHCl_3$); IR ν_{max} (liquid film) 1747, 1732 cm^{-1}. ^1H NMR (300 MHz) selected values δ_H: 7.73 (1H, s, H-2′); 7.63 (1H, d, *J*=7.9 Hz, H-6′); 7.28 (1H, d, *J*=8.7 Hz, H-4′); 7.06 (1H, dd, *J*=7.9 and 8.7 Hz, H-5′); 5.39 (1H, m, H-16); 5.17 (1H, br s, H-20a); 5.00 (1H, br s, H-20b); 3.67 (3H, s, –OMe); 3.60 (1H, d, *J*=14.2 Hz, H_2a-benzyl); 3.51 (1H, d, *J*=14.2 Hz, H_2b-benzyl); 3.02 (1H, s, H-18); 0.98 (3H, s, H_3-25); 0.89 (3H, s, H_3-24); 0.79 (3H, s, H_3-23); 0.78 (3H, s, H_3-21); 0.75 (3H, s, H_3-22). ^{13}C NMR (75.5 MHz) δ_C: 171.4 (C-19); 169.5 (CO–benzyl); 140.0 (C-17); 138.5 (C-4′); 136.7 (C-1′); 136.2 (C-2′); 130.3 (C-5′); 128.7 (C-6′); 114.3 (C-20); 94.4 (C-3′); 75.8 (C-16); 60.8 (C-9); 58.5 (C-18); 56.0 (C-5); 52.9 (C-14); 51.1 (–OMe); 42.2 (C-3); 41.8 (C-7); 41.4 (CH_2–benzyl); 40.2 (C-12); 39.8 (C-1); 39.5 (C-13); 37.5 (C-8); 37.3 (C-10); 33.4 (2C, C-4 and C-21); 27.0 (C-15); 21.3 (C-22); 18.7 (C-2); 18.0 (C-6); 17.4 (C-11); 17.1 (C-24); 16.3 (C-23); 14.1 (C-25). HRESIMS: *m/z* $(M+Na)^+$ 669.2405 (669.2417 calcd for $C_{34}H_{47}O_4INa$).

4.3.3. Radical relay halogenation of ester 19. K_2CO_3 (17 mg, 0.12 mmol) was added to a deoxygenated solution of ester **19** (15 mg, 0.024 mmol) in 2.5 mL of a mixture dichloromethane/*tert*-butanol (2:1). The resulting suspension was treated on stirring with 9.75 mg (0.036 mmol) of iodophenyldichloride.[19] The reaction mixture was irradiated at room temperature for 2 h with two filament lamps (200 W+100 W) on stirring. Following distillation of the solvent under reduced pressure provided a crude residue, which was treated with a mixture of dioxane (1.5 mL) and 10% KOH in methanol (1.5 mL) at 80 °C for 1 h. Usual work-up provided the crude product, which was submitted to flash chromatography on Si gel. Elution with 10% EtOAc in petroleum ether provided 5 mg (0.013 mmol, 52%) of ester **21**. Colorless viscous liquid; $[\alpha]_D^{25}$ −50.7 (*c* 0.15, $CHCl_3$); IR ν_{max} (liquid film) 1725 cm^{-1}. ^1H NMR (400 MHz) δ_H: 5.39 (1H, m, H-6); 5.06 (1H, br s, H-20a); 4.86 (1H, br s, H-20b); 4.40 (1H, m, H-16); 3.66 (3H, s, –OMe); 3.32 (1H, s, H-18); 1.99 (1H, dd, *J*=17.2 and 5.5 Hz, H-7a); 1.84 (1H, m, H-1a); 1.80 (1H, m, H-2a); 1.77 (1H, m, H-7b); 1.70 (2H, m, H_2-15); 1.63 (1H, m, H-12a); 1.60 (1H, m, H-14); 1.52 (2H, m, H_2-11); 1.48 (1H, m, H-12b); 1.47 (1H, m, H-3a); 1.45 (1H, m, H-2b); 1.22 (1H, m, H-3b); 1.18 (1H, m, H-9); 1.11 (3H, s, H_3-22); 1.09 (3H, s, H_3-23); 1.05 (3H, s, H_3-21); 1.04 (3H, s, H_3-25); 0.92 (1H, m, H-1b); 0.85 (3H, s, H_3-24). ^{13}C NMR (75.5 MHz) δ_C: 171.7 (C-19); 148.1 (C-5); 145.1 (C-17); 116.4 (C-6); 111.5 (C-20); 72.9 (C-16); 57.4 (C-18); 56.1 (C-9); 50.9 (2C, –OMe and C-14); 42.6 (C-7); 41.8 (C-3); 41.1 (C-1); 39.6 (2C, C-12 and C-13); 37.8 (C-10); 36.3 (C-8); 34.8 (C-4); 33.2 (C-21); 29.4 (2C, C-15 and C-22); 20.3 (C-23); 18.9 (C-11); 18.6 (C-2); 17.9 (C-24); 13.4 (C-25). HRESIMS: *m/z* $(M+Na)^+$ 423.2867 (423.2875 calcd for $C_{26}H_{40}O_3Na$).

4.3.4. Radical relay halogenation of ester 20. A solution of 83 mg (0.129 mmol) of ester **20** and 3.1 mg (0.013 mmol) dibenzoylperoxide in 12 mL CCl_4 was treated with 12.4 mL (0.154 mmol) SO_2Cl_2 and the reaction mixture refluxed for 5 h. Following distillation of the solvent under reduced pressure provided a crude residue, which was treated with a mixture of dioxane (1.5 mL) and 10% KOH in methanol (1.5 mL) at 80 °C for 1 h. Usual work-up provided the crude product, which was submitted to flash chromatography on Si gel. Elution with 10% EtOAc in petroleum ether provided 8 mg (0.02 mmol, 16%) of ester **21**.

4.3.5. Acetylation of 21. Compound **21** (7 mg) was dissolved in pyridine (1 mL) and treated with acetic anhydride (0.3 mL). After 12 h at room temperature, usual work-up provided pure acetate **22**. Colorless viscous liquid; $[\alpha]_D^{25}$ −49.5 (*c* 0.10, $CHCl_3$); IR ν_{max} (liquid film) 1739 cm^{-1}. ^1H NMR (400 MHz) δ_H: 5.44 (1H, m, H-16); 5.39 (1H, m, H-6); 5.20 (1H, br s, H-20a); 5.01 (1H, d, *J*=0.5 Hz, H-20b); 3.66 (3H, s, –OMe); 3.14 (1H, s, H-18); 2.05 (3H, s, –OAc); 1.97 (1H, dd, *J*=17.3 and 5.5 Hz, H-7a); 1.82 (1H, m, H-1a); 1.80 (2H, m, H-2a and H-15a); 1.70 (1H, m, H-15b); 1.65 (1H, m, H-7b); 1.62 (1H, m, H-12a); 1.54 (2H, m, H_2-11); 1.48 (1H, m, H-3a); 1.47 (1H, m, H-2b); 1.46 (1H, m, H-14); 1.37 (1H, m, H-12b); 1.22 (1H, m, H-3b); 1.17 (1H, m, H-9); 1.12 (3H, s, H_3-22); 1.09 (3H, s, H_3-23); 1.06 (3H, s, H_3-21); 1.05 (3H, s, H_3-25); 0.92 (1H, m, H-1b); 0.85 (3H, s, H_3-24). ^{13}C NMR (75.5 MHz) δ_C: 171.2 (C-19); 170.1 (–OAc); 149.0 (C-5); 140.2 (C-17); 116.2 (C-6); 114.4 (C-20); 74.9 (C-16); 58.4 (C-18); 56.1 (C-9); 52.0 (C-14); 51.0 (–OMe); 42.6 (C-7); 41.8 (C-3); 41.2 (C-1); 39.7 (C-12); 39.4 (C-13); 37.8 (C-10); 36.3 (C-8); 34.8 (C-4); 33.1 (C-21); 29.3 (C-22); 27.5 (C-15); 21.5 (–OAc); 20.3 (C-23); 18.9 (C-11); 18.6 (C-2); 17.8 (C-24); 13.6 (C-25). HRESIMS: *m/z* $(M+Na)^+$ 465.2958 (465.2981 calcd for $C_{28}H_{42}O_4Na$).

4.3.6. Allylic oxidation of acetate 22. Compound **22** (5 mg, 0.011 mmol) was dissolved in 0.5 mL acetonitrile and treated on stirring with a catalytic amount of CuI and 20 mL of a solution of *tert*-butylhydroperoxide in nonane. After stirring for 20 h at +50 °C under nitrogen, the reaction mixture was diluted with a satd solution of Na_2SO_3 (5 mL) and worked-up as usual. The crude product was submitted to flash chromatography affording 3 mg (0.007 mmol, 58%) of keto-diester **23**. Colorless viscous liquid; $[\alpha]_D^{25}$ −64.9 (*c* 0.16, $CHCl_3$); IR ν_{max} (liquid film) 1738, 1668 cm^{-1}. ^1H NMR (400 MHz) δ_H: 5.76 (1H, s, H-6); 5.47 (1H, m, H-16); 5.21 (1H, br s, H-20a); 4.95 (1H, d, *J*=0.7 Hz, H-20b); 3.66 (3H, s, –OMe); 3.25 (1H, s,

H-18); 2.84 (1H, m, H-15a); 2.10 (3H, s, –OAc); 2.05 (1H, dd, J=12.5 and 2.2 Hz, H-14); 1.96 (1H, m, H-1a); 1.87 (1H, m, H-2a); 1.67 (1H, m, H-15b); 1.62 (2H, m, H-3a and H-12a); 1.61 (1H, m, H-9); 1.60 (3H, m, H_2-11 and H-2b); 1.35 (2H, m, H-3b and H-12b); 1.27 (3H, s, H_3-23); 1.20 (3H, s, H_3-22); 1.14 (3H, s, H_3-21); 1.13 (3H, s, H_3-24); 1.10 (3H, s, H_3-25); 1.03 (1H, ddd, J=13.0, 12.7, and 3.8 Hz, H-1b). ^{13}C NMR (75.5 MHz) δ_C: 205.7 (C-7); 171.2 (2C, C-5 and C-19); 169.9 (–OAc); 140.4 (C-17); 121.4 (C-6); 114.5 (C-20); 74.7 (C-16); 58.8 (C-18); 56.4 (C-9); 51.0 (–OMe); 46.7 (C-8); 44.1 (C-14); 41.0 (C-1); 40.7 (C-3); 39.8 (C-10); 39.4 (C-13); 38.9 (C-12); 37.2 (C-4); 32.3 (C-21); 30.1 (C-15); 28.6 (C-22); 21.5 (–OAc); 20.4 (C-23); 18.6 (C-2); 18.3 (C-11); 16.2 (C-24); 15.1 (C-25). HRESIMS: m/z $(M+Na)^+$ 479.2756 (479.2773 calcd for $C_{28}H_{40}O_5Na$).

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