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Natural product synthesis from (8a*R*)- and (8a*S*)-bicyclofarnesols: synthesis of (+)-wiedendiol A, (+)-norsesterterpene diene ester and (−)-subersic acid

Yuusuke Arima, Masako Kinoshita and Hiroyuki Akita*

School of Pharmaceutical Sciences, Toho University, 2-2-1, Miyama, Funabashi, Chiba 274-8510, Japan

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Abstract—Both enantiomers (8a*R*)-**7** and (8a*S*)-**7** of bicyclofarnesol were synthesized from the enzymatic resolution products (1*R*,4a*R*,8a*R*)-1,2,3,4,4a,5,6,7,8,8a-decahydro-5,5,8a-trimethyl-2-oxo-*trans*-naphthalene-1-methanol-2-ethylene acetal (8a*R*)-**5** (98% ee) and acetate of (1*S*,4a*S*,8a*S*)-1,2,3,4,4a,5,6,7,8,8a-decahydro-5,5,8a-trimethyl-2-oxo-*trans*-naphthalene-1-methanol-2-ethylene acetal (8a*S*)-**6** (>99% ee), respectively. The formal synthesis of (+)-wiedendiol **1** was achieved via a coupling reaction of an ate complex derived from 1,2,4-trimethoxybenzene with allyl bromide (8a*S*)-**8** derived from (8a*S*)-**7**. The total synthesis of (+)-norsesterterpene diene ester **2** was achieved, based on the synthesis of (13*E*,10*S*)-α,β-unsaturated aldehyde **12**, derived from (8a*S*)-**7**, followed by the selective construction of the (3*E*,5*E*)-diene moiety including a C(2)-stereogenic centre in (+)-**2**. The total synthesis of (−)-subersic acid **3** was carried out based on a Stille coupling between allyl trifluoroacetate congener **25c**, derived from (8a*R*)-**7**, corresponding to the diterpene part, and aryl stannane congener **26** in the presence of Pd catalyst and CuI as an additive.

1. Introduction

There are many natural products containing the 2,5,5,8a-tetramethyl-3,4,4a,5,6,7,8,8a-octahydro-naphthalen-1-yl]-methylene skeleton. Typical among these are (+)-wiedendiol A **1**,[1] (+)-norsesterterpene diene ester **2**[2] (−)-subersic acid **3**[3] (Scheme 1). For the synthesis of these compounds, (8a*R*)- and (8a*S*)-bicyclofarnesols **7** are desirable starting materials. The conversion of the natural product (−)-sclareol to (8a*S*)-**7**[4] and the synthesis of (8a*R*)-**7**,[5] derived from (3*S*)-2,2-dimethyl-3-hydroxy-cyclohexanone, have been reported. Meanwhile, both (8a*R*)-**7** and (8a*S*)-**7** were obtained based on the optical resolution of β-keto ester (±)-**4** using 1,4-di-*O*-benzyl-L-threitol as a chiral auxiliary.[6] In addition, the lipase-assisted resolution of the racemic primary alcohol (±)-**5**, derived from (±)-**4**, was reported by us to give (8a*S*)-acetate **6** (49%, >99% ee) and (8a*R*)-primary alcohol **5** (49%, 98% ee).[7] This method of enzymatic resolution was found to be effective, and the *E*-value was estimated to be 921. Conversion of (8a*R*)-**5** to (8a*R*)-**4** was achieved[7] by a reported procedure,[6] and (8a*R*)-**7** was obtained from (8a*R*)-**4** by a reported procedure[5,6] in 74% overall yield (three steps). Enantiomer (8a*S*)-**7** was also obtained from (8a*S*)-**6** in the same way in which (8a*R*)-**7** was prepared from (8a*R*)-**5** (Scheme 1). Herein we report concise syntheses of (+)-wiedendiol A **1** and (+)-norsesterterpene diene ester **2** from (8a*S*)-**7**, and (−)-subersic acid (**3**) from (8a*R*)-**7**.

2. Formal synthesis of (+)-wiedendiol A 1

Wiedendiol A **1**, which was isolated from the marine sponge *Xestospongia wiedenmayeri*, inhibits cholesteryl ester transfer protein (CETP). The first synthesis of **1** was achieved based on the condensation of the drimanic aldehyde obtained from (−)-sclareol with the aryllithium derived from 3,4-dibenzyloxy anisole.[4b] A straightforward synthesis of wiedendiol A analogue **11** from (8a*S*)-**7** is shown in Scheme 2.

The reaction of an ate complex **10** derived from 1,2,4-trimethoxybenzene **9** with allyl bromide (8a*S*)-**8** obtained by treatment of (8a*S*)-**7** with PBr_3 gave the desired product

* Corresponding author. Tel.: +81 047 472 1805; fax: +81 047 476 6195; e-mail: akita@phar.toho-u.ac.jp

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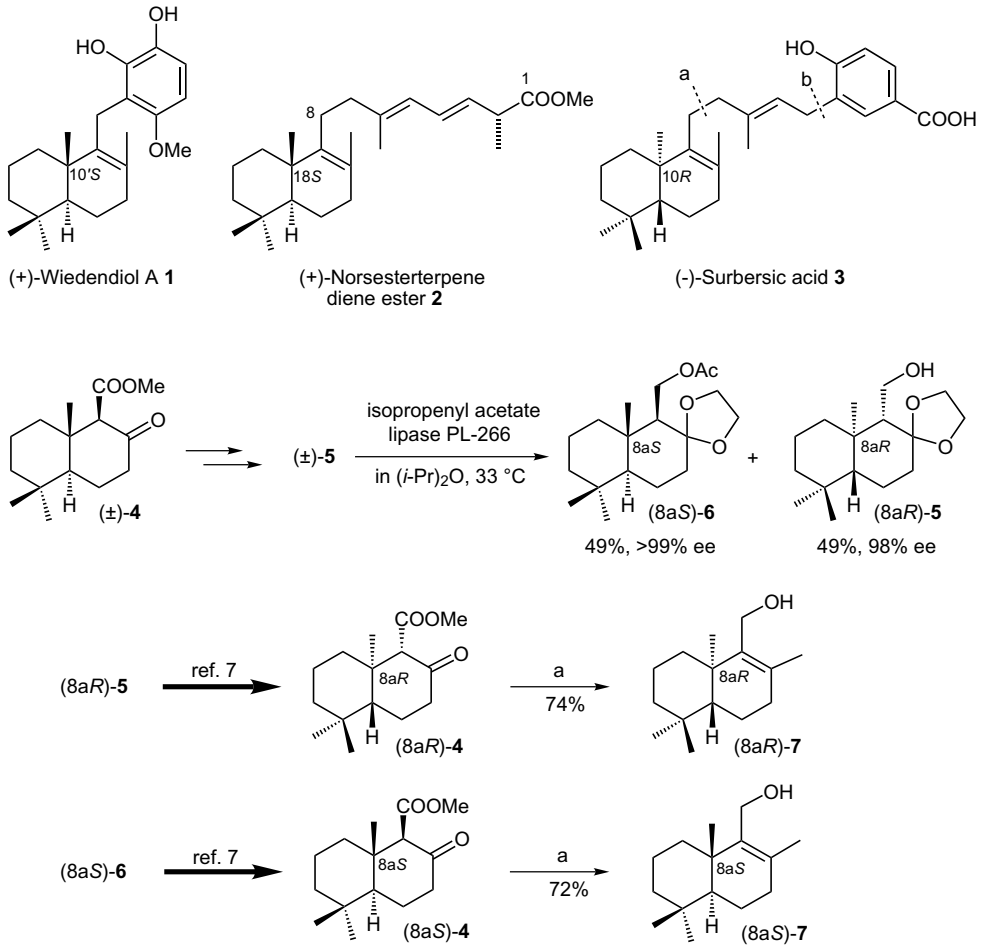
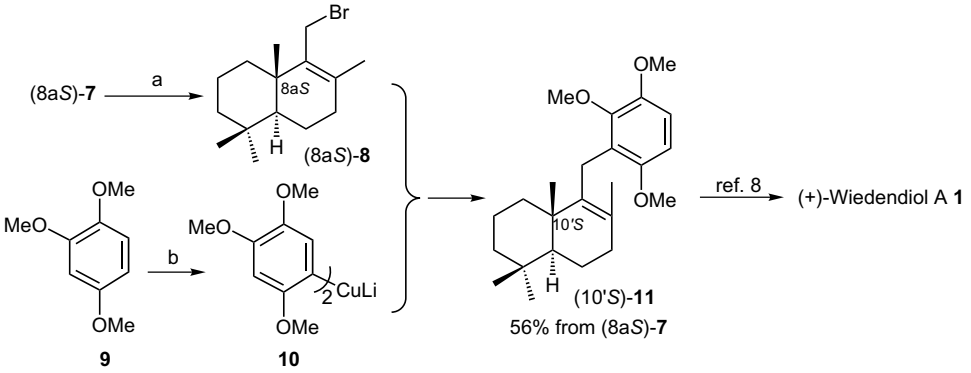


Scheme 1. Reagents and conditions: (a) (1) $(EtO)_2P(O)Cl/NaH/THF$; (2) Me_2CuLi/Et_2O; (3) $(^iBu)_2AlH$/toluene.



Scheme 2. Reagents and conditions: (a) PBr_3/pyridine/Et_2O; (b) (1) ^{t}BuLi/TMEDA/Et_2O; (2) CuCN.

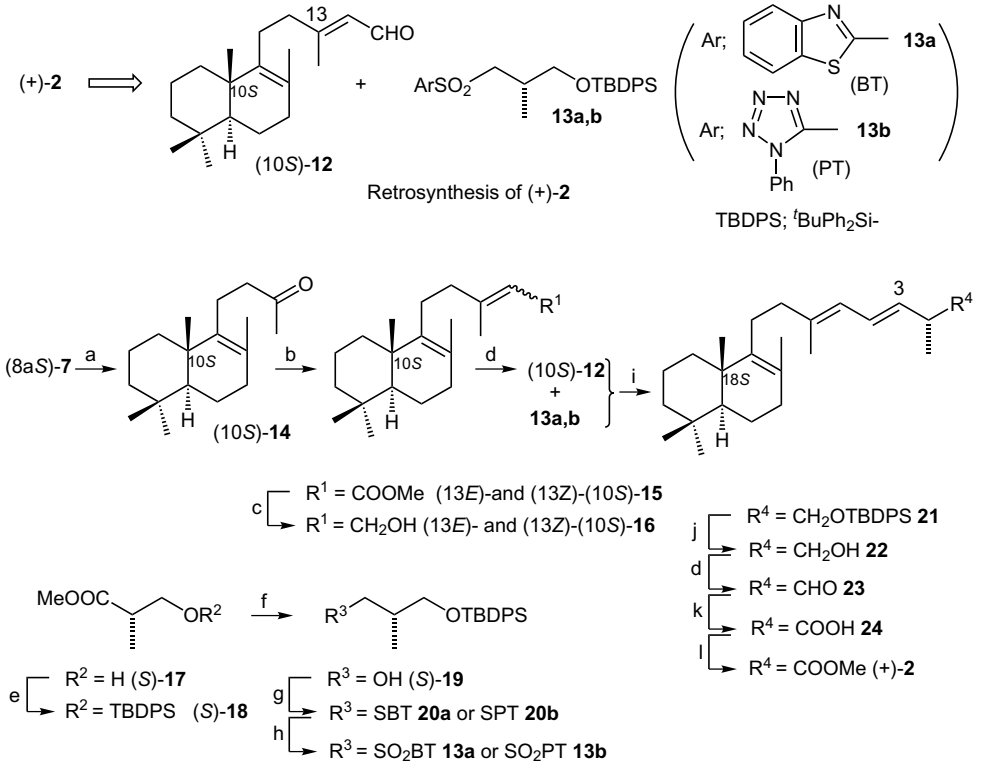
{(10′*S*)-**11**, $[\alpha]_D^{22} = +69.7$ (*c* 1.71, $CHCl_3$)} in 56% yield from (8a*S*)-**7**. The spectral data (^{1}H NMR) of synthetic (10′*S*)-**11** was identical to that previously reported.[8] The specific rotation of synthetic (10′*S*)-**11** was in accordance with that of the reported sample {$[\alpha]_D^{25} = +72.0$ (*c* 1.75, $CHCl_3$)}.[8] The synthesis of wiedendiol A **1** from (10′*S*)-**11** has already been achieved based on selective demethylation.[8]

3. Synthesis of (+)-norsesterterpene diene ester 2

(+)-Norsesterterpene diene ester **2** was originally isolated from an Australian marine sponge, *Latrunculia brevis*, and its structure was determined by detailed spectroscopic analysis, chemical derivatization and degradation.[2] The synthesis of **2** was achieved by the preparation of the chiral *E*,*E*-diene part corresponding to the side chain of **2** and

addition to (−)-2,5,5,8a-tetramethyl- octahydronaphthalen-1-one, derived from (−)-carvone.[9] The retrosynthesis of (+)-**2** is shown in Scheme 3. Our synthetic plan for (+)-**2** is based on synthesis of (13*E*,10*S*)-α,β-unsaturated aldehyde **12**, followed by the selective construction of the (3*E*,5*E*)-diene moiety including a C(2)-stereogenic centre in (+)-**2**.

Treatment of (8a*S*)-**7** with PBr_3 followed by acetoacetic ester synthesis gave methyl ketone (10*S*)-**14** [40% overall yield from (8a*S*)-**7**], which was subjected to a Horner–Emmons reaction to afford a 7:2 mixture of (13*E*)- and (13*Z*)-α,β-unsaturated esters **15**. DIBAL reduction of this mixture gave a mixture of (13*E*)- and (13*Z*)-allylic alcohol **16**, which was separated to give (13*E*)-**16** [70% overall yield from (10*S*)-**14**] and (13*Z*)-**16** [20% overall yield from (10*S*)-**14**]. The 13*E*-geometry of **16** was confirmed by an NOE enhancement (1.3%) between the C(13)-methyl group and the C(15)-methylene group. Dess–Martin oxidation of (13*E*)-**16** afforded the desired aldehyde (10*S*)-**12** in 89% yield. For selective construction of the (3*E*,5*E*)-diene moiety including a C(2) stereogenic centre in (+)-**2**, a modified Julia coupling method[10] using a chiral sulfone, (*S*)-**13a** or (*S*)-**13b**, was thought likely to be effective. Commercially available methyl (*S*)-3-hydroxy-2-methylpropionate **17** was used for the synthesis of (*S*)-**13a** and (*S*)-**13b** as the starting materials. Silylation {(*S*)-**18**, 90% yield} of (*S*)-**17** followed by reduction with $LiBH_4$ gave (*S*)-alcohol **19** (98% yield), which was treated with 2-mercaptobenzothiazole (BTSH) in the presence of Ph_3P and diethylazodicarboxylate to provide (*S*)-sulfide **20a** (82% yield). Oxidation of (*S*)-**20a** gave the desired sulfone **13a** in 80% yield. Treatment of (*S*)-**19** with 1-phenyl-1*H*-tetrazole-5-thiol (PTSH) in the presence of Ph_3P and diethylazodicarboxylate provided the (*S*)-sulfide **20b** (96% yield). Oxidation of (*S*)-**20b** gave the desired sulfone **13b** in 59% yield. A modified Julia coupling of (10*S*)-**12** and **13a** in the presence of lithium bis(trimethylsilyl)amide (LHMDS) gave a 6.2:1 (*E*:*Z*) mixture (73% yield) of (3*E*)-**21** and (3*Z*)-**21**, while coupling of (10*S*)-**12** and **13b** in the presence of LHMDS afforded a 11:1 (*E*:*Z*) mixture (83% yield) of (3*E*)-**21** and (3*Z*)-**21**. Deprotection of the silyl group in an 11:1 mixture of (3*E*)-**21** and (3*Z*)-**21** followed by chromatographic separation provided the desired alcohol (3*E*)-**22** (81% yield); this was then subjected to a Dess–Martin oxidation to give the corresponding aldehyde **23** in 53% yield. Oxidation of **23** in *tert*-BuOH with $NaClO_2$ in the presence of 2-methyl-2-butene and NaH_2PO_4 gave carboxylic acid **24**, which was treated with CH_2N_2 to afford the corresponding methyl ester (+)-**2** {$[\alpha]_D^{25} = +12.4$ (*c* 0.55, $CHCl_3$)} in 33% overall yield. The spectral data (^1H and ^{13}C NMR) of synthetic (+)-**2** were identical to those previously reported for (+)-**2**,[2] including the specific rotation {$[\alpha]_D = +13.3$ (*c* 2.55, $CHCl_3$)}.[2]



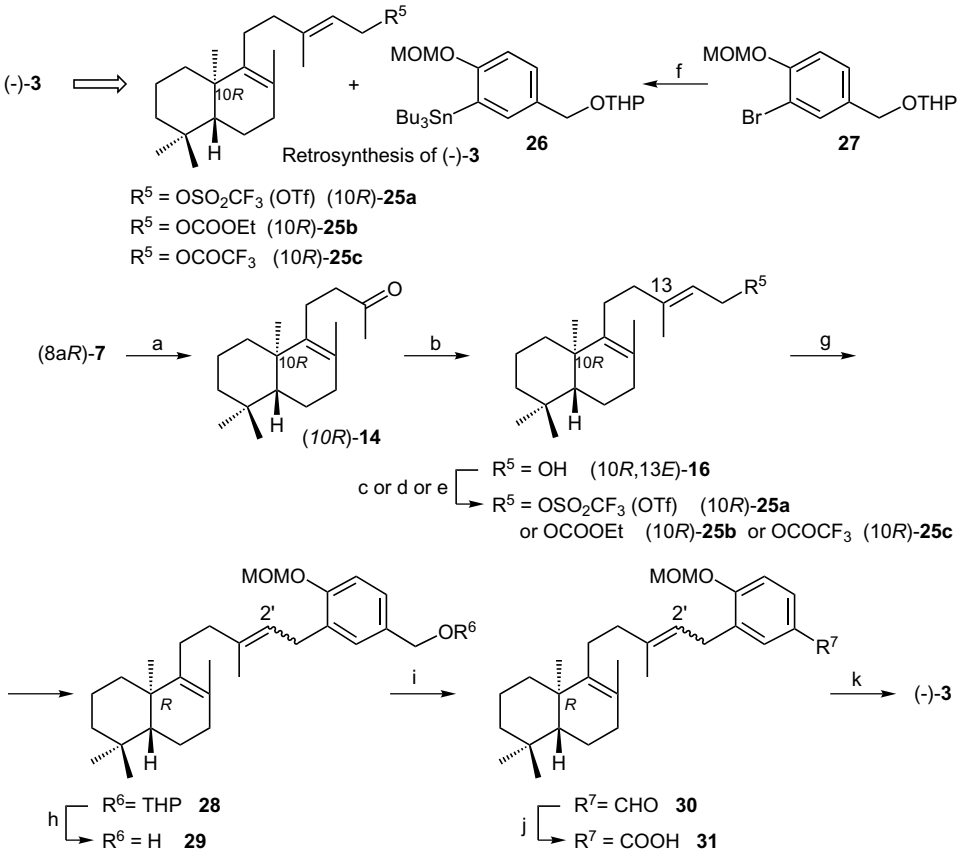
Scheme 3. Reagents and conditions: (a) (1) PBr_3/pyridine/Et_2O; (2) methyl acetoacetate/^{t}BuOK/DMSO; (3) 2 M NaOH/MeOH; (b) (1) $(EtO)_2P(O)CH_2COOMe$/NaH/THF; (c) (1) $(^iBu)_2AlH$/toluene; (2) separation (d) Dess–Martin reagent/CH_2Cl_2; (e) ^{t}BuPh$_2$SiCl/imidazole/DMF; (f) $LiBH_4$; (g) for **20a**: BTSH/EtOOC–N=N=COOEt/Ph_3P/THF for **20b**: PTSH/EtOOC–N=N–COOEt/Ph_3P/THF; (h) $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$/30% H_2/EtOH; (i) $(Me_3Si)_2N^-Li^+$ (LHMDS)/THF; (j) (1)$^tBu_4N^+F^-$(TBAF)/THF; (2) separation; (k) $NaClO_2$/2-methyl-2-butene/NaH_2PO_4/^{t}BuOH/H_2O; (l) CH_2N_2/Et_2O.

4. Synthesis of (−)-subersic acid 3

(−)-Subersic acid **3**, which was originally isolated from the Papua New Guinean sponge *Suberea* sp., an inhibitor of human 15-lipoxygenase.[3] The structure of (−)-**3** was determined by extensive NMR analysis, and the (5*R*,10*R*)-absolute structure of (−)-**3** was deduced based on the positive molar rotation of (−)-**3**.[3] The first synthesis of (−)-**3** was achieved based on the carbon–carbon bond formation at the dotted line **a** (Scheme 1) by coupling of an aryl sulfone corresponding to the sesquiterpene part and an allyl bromide corresponding to the side chain in (−)-**3**.[5] This synthesis made it possible to determine the absolute structure of (−)-**3**.[5] Meanwhile, the synthesis of (+)-**3** from the natural product sclareol was carried out via carbon–carbon bond formation at the dotted line **b** (Scheme 1) between an allyl bromide part, corresponding to the left-hand side of (−)-**3**, and an aryl part.[11] Our synthetic plan is shown in Scheme 4; this also involves carbon–carbon bond formation at the dotted line **b**. In this way we attempted to improve the coupling yield, since the yield in previous case[11] was 26%.

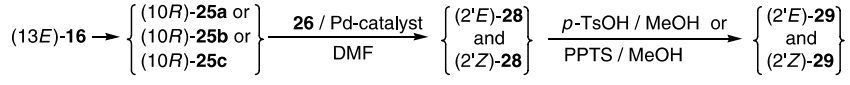
In order to carry out a Stille coupling between allyl triflate (10*R*)-**25a**, allyl carbonate (10*R*)-**25b** or allyl trifluoroacetate (10*R*)-**25c** and aryl stannane congener **26**, derived from the previously reported aryl bromide congener **27**,[11] the synthesis of (10*R*,13*E*)-allyl alcohol congener **16** from (8a*R*)-**7** was carried out in the same way as the preparation of (10*S*,13*E*)-**16** from (8a*S*)-**7** (Scheme 3). Treatment of **27**[11] with *tert*-BuLi followed by the addition of *n*-Bu_3SnCl gave the desired stannane congener **26** in 62% yield. A Stille coupling reaction between (10*R*)-**25a**, (10*R*)-**25b** or (10*R*)-**25c** and aryl stannane congener **26** in the presence of Pd catalyst was carried out, and results are shown in Table 1.

When the three substrates were individually subjected to Stille coupling using tetrakis(triphenyl-phophine)palladium(0) ($Pd(Ph_3P)_4$) or tris(dibenzylideneacetone)dipalladium(0)–chloroform adduct [$Pd_2(dba)_3{\cdot}CHCl_3$] as a Pd catalyst, no reaction occurred as shown in entries 1–4 and 6. When the reaction of allyl carbonate **25b** and **26** was carried out using $Pd_2(dba)_3{\cdot}CHCl_3$ and LiCl as an additive at 100 °C, a 1:1 mixture of the coupled products (2′*E*)-**29** and (2′*Z*)-**29** was obtained in 44% overall yield after deprotection of the tetrahydropyranyl group (entry 5). The *E*/*Z* ratio was calculated based on the NMR integrated values of the olefinic proton (δ 5.30 (t) and 5.24 (t)). In contrast, when the reaction of allyl trifluoroacetate **25c** and **26** was carried out using $Pd_2(dba)_3{\cdot}CHCl_3$ and CuI as an additive at rt, a ca. 7:1 mixture [(2′*E*)-**29**/(2′*Z*)-



Scheme 4. Reagents and conditions: (a) (1) PBr_3/pyridine/Et_2O; (2) methyl acetoacetate/^{t}BuOK/DMSO; (3) 2 M NaOH/MeOH; (b) (1) $(EtO)_2P(O)CH_2COOMe$/NaH/THF; (2) $(^i Bu)_2AlH$/toluene; (3) separation; (c) Tf_2O/pyridine; (d) ClCOOEt/pyridine; (e) $(CF_3CO)_2O$/2,6-lutidine/CH_2Cl_2; (f) (1) ^{t}BuLi/THF; (2) Bu_3SnCl; (g) **26**/$Pd_2(dba)_3{\cdot}CHCl_3$/LiCl/DMF or **26**/$Pd_2(dba)_3{\cdot}CHCl_3$/CuI/DMF; (h) *p*-TsOH/MeOH or PPTS/MeOH; (i) MnO_2; (j) $NaClO_2$/2-methyl-2-butene/NaH_2PO_4/^{t}BuOH/H_2O; (k) (1) 6 M HCl/THF; (2) separation.

Table 1. Stille coupling



Entry	Substrate	Catalyst	Additive	Solvent	Conditions	(2′*E*)-**29** and (2′*Z*)-**29** yield[a] (%, *E*:*Z*)
1	(10*R*)-**25a**	$Pd(Ph_3P)_4$	CuI	DMF	rt, 7 d	NR[b]
2	(10*R*)-**25a**	$Pd(Ph_3P)_4$	LiCl	DMF	40 °C, 4 d	NR
3	(10*R*)-**25b**	$Pd(Ph_3P)_4$	CuI	DMF	100 °C, 4 d	NR
4	(10*R*)-**25b**	$Pd_2(dba)_3{\cdot}CHCl_3$	CuI	DMF	rt, 6 d	NR
5	(10*R*)-**25b**	$Pd_2(dba)_3{\cdot}CHCl_3$	LiCl	DMF	100 °C, 4 h	44 (*E*:*Z* = 1:1)
6	(10*R*)-**25c**	$Pd(Ph_3P)_4$	CuI	DMF	rt, 24 h	NR
7	(10*R*)-**25c**	$Pd_2(dba)_3{\cdot}CHCl_3$	CuI	DMF	rt, 24 h	54 (*E*:*Z* = 7:1)

[a] Overall yield from (13*E*)-**16**.
[b] No reaction.

29 = 7:1] of the coupled products was obtained in 54% overall yield (entry 7). The 2′*E*-geometry of the major product (2′*E*)-**29** was confirmed by NOE enhancement (4.4%) between the C(3′)-methyl group and the C(1′)-methylene group. Stille coupling between the same (*E*)-allyl carbonate congener[12] as **25b** and pyridine-containing stannane[12] in the presence of $Pd_2(dba)_3$ and LiCl in DMF was reported to give a ca. 2.5:1 mixture of the coupled products (*E*:*Z* = ~2.5:1), from which the desired (*E*)-form was obtained in 55% yield.[12] Manganese(IV) oxide (MnO_2) oxidation of this 7:1 mixture gave a ca. 8:1 mixture of the corresponding aldehydes (2′*E*)-**30** and (2′*Z*)-**30** in 92% yield. Oxidation of the aldehyde mixture in *tert*-BuOH with $NaClO_2$ in the presence of 2-methyl-2-butene and NaH_2PO_4 gave a 9:1 mixture of the corresponding carboxylic acids **31** in 53% yield, which was treated with 6 M aqueous HCl to afford a 9:1 mixture of the (2′*E*)- and (2′*Z*)-natural products **3**. Finally, this mixture was subjected to preparative HPLC to afford (−)-**3** $\{[\alpha]_D^{24} = -46.7$ (*c* 0.17, $CHCl_3)\}$ in 69% yield. The spectral data (^1H and ^{13}C NMR) of synthetic (−)-**3** were identical to those of the reported compound[3] including the specific rotation $\{[\alpha]_D^{22} = -46.0$ (*c* 0.5, $CHCl_3)\}$.[3]

5. Conclusion

Two enantiomers (8a*R*)-**7** and (8a*S*)-**7** of bicyclofarnesol were synthesized from the enzymatic resolution products 2-ethylene acetal alcohol (8a*R*)-**5** (98% ee) and 2-ethylene acetal acetate (8a*S*)-**6** (>99% ee), respectively. The formal synthesis of (+)-wiedendiol **1** was achieved by the coupling reaction of an ate complex derived from 1,2,4-trimethoxybenzene with allyl bromide (8a*S*)-**8** derived from (8a*S*)-**7**. The total synthesis of (+)-norsesterterpene diene ester **2** was achieved based on the synthesis of (13*E*,10*S*)-α,β-unsaturated aldehyde **12**, derived from (8a*S*)-**7**, followed by selective construction of the (3*E*,5*E*)-diene moiety including a C(2) stereogenic centre in (+)-**2**. The total synthesis of (−)-subersic acid **3** was carried out based on the Stille coupling between allyl trifluoroacetate congner **25c** derived from (8a*R*)-**7**, corresponding to the diterpene part, and aryl stannane congener **26** in the presence of a Pd catalyst and CuI as an additive.

6. Experimental

6.1. Methods and results

All melting points were measured on a Yanaco MP-3S micro melting point apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on JEOL AL 400 spectrometer in $CDCl_3$. Carbon substitution degrees were established by DEPT pulse sequence. The fast atom bombardment mass spectra (FAB MS) were obtained with JEOL JMS 600H spectrometer. IR spectra were recorded with a JASCO FT/IR-300 spectrometer. The preparative HPLC systems were composed of a detector (SPD-M10 AVP (SHIMADZU)) and a pump (PU-980 (JASCO)). HPLC analysis conditions were as follows; column: YMC ODS-A (4.6 × 250 mm), solvent: 90% MeOH including 0.06% TFA, flow rate: 1 mL/min. Optical rotations were measured with a JASCO DIP-370 digital polarimeter. All evaporations were performed under reduced pressure. For column chromatography, silica gel (Kieselgel 60) was employed.

6.2. (−)-[(4a*R*,8a*R*)-2,5,5,8a-Tetramethyl-3,4,4a,5,6,7,8,8a-octahydronaphthalen-1-yl]methanol 7

(i) To a suspension of NaH (55% in mineral oil) in THF (100 mL) was added a solution of (8a*R*)-**4** (11.0 g, 43 mmol) in THF (10 mL) at 0 °C and the reaction mixture was stirred for 1 h at 80 °C. To the above reaction mixture was added diethyl chlorophosphate (9.02 g, 52.3 mmol) at 0 °C, and the reaction mixture was stirred for 7 h at rt. The reaction mixture was diluted with brine and extracted with Et_2O. The organic layer was dried over $MgSO_4$ and evaporated to give a crude oil, which was chromatographed on silica gel (400 g, *n*-hexane/AcOEt = 1:1) to give the reported enol phosphonate (14.89 g, 88%) as a colourless oil. $[\alpha]_D^{25} = -61.0$ (*c* 1.02, $CHCl_3$); ^1H NMR spectra were identical with those of the reported data.[3] (ii) To a suspension of CuI (22.0 g, 115 mmol) in Et_2O (50 mL) was added dropwise a 1.2 M MeLi in Et_2O solution (193 mL, 231.6 mmol) at −78 °C and the reaction mixture was stirred for 30 min at the same temperature. A solution of the above enol phosphonate (14.89 g) in Et_2O (50 mL) was added dropwise to the above Me_2CuLi solution at

−78 °C and the reaction mixture was stirred for 12 h at 0 °C. The reaction mixture was diluted with 10% aqueous NH_4Cl and filtered with the aid of Celite. The filtrate was extracted with Et_2O and dried over $MgSO_4$. Evaporation of the organic solvent gave a crude oil, which was chromatographed on silica gel (200 g, *n*-hexane/AcOEt = 50:1) to give the reported α,β-unsaturated ester (8.346 g, 87%) as a colourless oil. $[\alpha]_D^{24} = -93.4$ (*c* 1.14, $CHCl_3$); ^1H NMR spectra were identical with those of the reported data.[3] (iii) To a solution of the above α,β-unsaturated ester (8.346 g, 33.4 mmol) was added 1 M diisobutylaluminium hydride (Dibal) in toluene solution (80 mL, 80 mmol) at −78 °C and the reaction mixture was stirred for 5 h at the same temperature. MeOH (80 mL) was added to the reaction mixture at −20 °C. The reaction mixture was diluted with 2 M aqueous HCl, extracted with Et_2O and dried over $MgSO_4$. Evaporation of the organic solvent gave a crude oil, which was chromatographed on silica gel (300 g, *n*-hexane/AcOEt = 20:1) to give the reported (8a*R*)-cyclofarnesol **7** (7.188 g, 97%). $[\alpha]_D^{24} = -110.0$ (*c* 0.3, $CHCl_3$); ^1H NMR spectra were identical with those of the reported data.[3]

6.3. (+)-[(4a*S*,8a*S*)-2,5,5,8a-Tetramethyl-3,4,4a,5,6,7,8,8a-octahydronaphthalen-1-yl]methanol 7

(8a*S*)-Cyclofarnesol **7** was synthesized from (8a*S*)-**4** in 72% overall yield in the same way as for preparation of (8a*R*)-**7** from (8a*R*)-**4**. (8a*S*)-**7**: $[\alpha]_D^{24} = -110.0$ (*c* 0.15, $CHCl_3$). ^1H NMR spectra of (8a*S*)-**7** were identical with those of (8a*R*)-**7**.

6.4. (+)-1,2,4-Trimethoxy-3-[5′*S*,10′*S*,8′(9′)-drimen-11′-yl]benzene 11

(i) To a solution of (8a*S*)-cyclofarnesol **7** (0.504 g, 2.26 mmol) and pyridine (0.190 g, 2.4 mmol) in Et_2O (5 mL) was added phosphorus tribromide (PBr_3; 0.25 mL, 2.6 mmol) at 0 °C and the reaction mixture was stirred for 10 min. The reaction mixture was diluted with brine and extracted with Et_2O. The organic layer was dried over $MgSO_4$ and evaporated to give crude **8** (0.648 g), which was used for the next reaction without further purification. (ii) To a solution of 1,2,4-trimethoxybenzene **9** (0.946 g, 5.6 mmol) and TMEDA (5 mL, 33 mmol) in Et_2O (10 mL) was added *tert*-BuLi (1.64 M in pentane solution, 3.5 mL, 5.7 mmol) at −78 °C and the reaction mixture was stirred for 1 h at 0 °C. (iii) To dry CuCN (0.503 g, 5.6 mmol) was added the above lithium anion solution at 0 °C and the reaction mixture was stirred for 1.5 h at room temperature. A solution of crude **8** in Et_2O (10 mL) was added to the generated ate complex **10** and the whole mixture was stirred for 1.5 h at room temperature. The reaction mixture was diluted with H_2O and filtered with the aid of Celite after which the filtrate was extracted with Et_2O. The organic layer was washed with brine and dried over $MgSO_4$. Evaporation of the organic solvent gave a residue, which was chromatographed on silica gel (30 g) to give bromide **8** (0.120 g, 26% overall yield from (*S*)-cyclofarnesol) from *n*-hexane elution and **11** (0.482 g, 56% overall yield from (*S*)-cyclofarnesol) from *n*-hexane/AcOEt = 100:1 elution. A part of **11** was crystallized from MeOH to afford colourless prism (10′*S*)-**11**. (+)-(10′*S*)-**11**: mp 53–55 °C, $[\alpha]_D^{22} = +69.7$ (*c* 1.71, $CHCl_3$); IR (neat): 2938, 1591, 1476, 1252, 1095, 719 cm^{-1}; ^1H NMR: δ 0.80 (3H, s), 0.85 (3H, s), 0.92 (3H, s), 1.09–1.16 (3H, m), 1.31–1.60 (5H, m), 1.47 (3H, s), 1.88 (1H, br d, *J* = 13.5 Hz), 1.99–2.03 (2H, m), 3.37 (1H, d, *J* = 16 Hz), 3.48 (1H, d, *J* = 16 Hz), 3.72 (3H, s), 3.72 (3H, s), 3.79 (3H, s), 6.49 (1H, d, *J* = 9 Hz), 6.67 (1H, d, *J* = 9 Hz). ^{13}C NMR: δ 19.2 (t), 19.2 (t), 20.1 (q), 20.5 (q), 21.8 (q), 23.3 (t), 33.3 (s), 33.5 (q), 34.8 (t), 36.8 (t), 39.6 (s), 41.8 (t), 51.9 (d), 56.0 (q), 56.2 (q), 60.1 (q), 105.6 (d), 109.3 (d), 126.1 (s), 126.4 (s), 138.4 (s), 147.3 (s), 148.3 (s), 152.5 (s). Anal. Calcd for $C_{24}H_{36}O_3$: C, 77.38; H, 9.74. Found: C, 77.20; H, 9.72.

6.5. 14,15-Bisnor-[8(9),5*S*,10*S*]-labdaen-13-one 14

(i) To a solution of the crude bromide (8aS)-**8** (2.56 g) obtained from (8a*S*)-cyclofarnesol **7** (2.04 g, 9.17 mmol) and methyl acetoacetate (5.34 g, 46 mmol) in DMSO (20 mL) was added *tert*-BuOK (1.42 g, 13.5 mmol) and whole mixture was stirred for 12 h at 60 °C. The reaction mixture was diluted with brine and extracted with Et_2O. The organic layer was dried over $MgSO_4$ and evaporated to give a residue, which was chromatographed on silica gel (50 g, *n*-hexane/AcOEt = 10:1) to give the α-substituted methyl acetoacetate congener (1.33 g) from *n*-hexane/AcOEt = 100:1 elution. (ii) A mixture of the above congener (1.33 g) and aqueous 2 M NaOH solution (10 mL) was stirred for 3 h at 100 °C. The reaction mixture was evaporated to give a residue, which was diluted with brine and extracted with Et_2O. The organic layer was dried over $MgSO_4$ and evaporated to give a residue, which was chromatographed on silica gel (50 g, *n*-hexane/AcOEt = 50:1) to give a colourless oil (5*S*,10*S*)-**14** [0.98 g, 40% overall yield from (8a*S*)-**7**]. (5*S*,10*S*)-**14**: $[\alpha]_D^{24} = +74.3$ (*c* 1.12, $CHCl_3$); IR (neat): 1715 cm^{-1}; ^1H NMR: δ 0.80 (3H, s), 0.85 (3H, s), 0.91 (3H, s), 1.04–1.10 (3H, m), 1.34–1.49 (3H, m), 1.50 (3H, s), 1.55–1.65 (2H, m), 1.75 (1H, br d, *J* = 11 Hz), 1.89–1.99 (2H, m), 2.01–2.15 (1H, m), 2.10 (3H, s), 2.24–2.30 (1H, m), 2.43–2.49 (2H, m). ^{13}C NMR: δ 19.1 (t), 19.1 (t), 19.5 (q), 20.1 (q), 21.7 (t), 21.8 (q), 29.9 (q), 33.4 (s), 33.4 (q), 33.7 (t), 37.0 (s), 39.2 (s), 41.8 (t), 44.7 (t), 52.0 (d), 126.4 (s), 139.1 (s), 208.6 (s). Anal. Calcd for $C_{18}H_{30}O$: C, 82.38; H, 11.52. Found: C, 82.24; H, 11.63. FAB MS *m*/*z*: 285 (M^++Na).

6.6. [8(9),5*S*,10*S*,13*E*]-Labdadien-15-ol 16 and [8(9),5*S*,10*S*,13*Z*]-labdadien-15-ol 16

(i) 55% NaH in oil (0.888 g, 20 mmol) was washed with *n*-hexane and methyl diethylphosphonoacetate (5.37 g, 25.6 mmol) was added to a suspension of the above NaH in THF (80 mL). The reaction mixture was stirred for 1 h at room temperature and a solution of (5*S*,10*S*)-**14** (1.24 g, 4.7 mmol) in THF (20 mL) was added to the above reaction mixture. After the whole mixture was stirred for 12 h at room temperature, it was diluted with brine at 0 °C and extracted with Et_2O. The organic layer was dried over $MgSO_4$ and evaporated to give a residue, which was chromatographed on silica gel (50 g, *n*-hexane/AcOEt = 100:1) to give a 7:2 mixture of α,β-unsaturated esters **15**

(1.49 g) as a colourless oil. (ii) To a solution of the above mixture (1.49 g) in toluene (30 mL) was added 1 M diisobutylaluminium hydride (Dibal) in toluene solution (15 mL, 15 mmol) at −78 °C and the mixture was stirred for 10 min at the same temperature. To a reaction mixture at −20 °C was added MeOH (30 mL) and whole mixture was diluted with 2 M aqueous HCl, extracted with Et_2O. The organic layer was dried over $MgSO_4$ and evaporated to give a residue, which was chromatographed on silica gel (50 g, *n*-hexane/AcOEt = 10:1) to afford (13*Z*)-**16** (0.276 g, 20% overall yield from **14**) as a colourless oil and (13*E*)-**16** (0.947 g, 70% overall yield from **14**) as a colourless oil in elution order. (13*Z*)-**16**: $[\alpha]_D^{23} = +71.5$ (*c* 0.99, $CHCl_3$); IR (neat): 3326, 1666 cm^{-1}; ^1H NMR: δ 0.81 (3H, s), 0.87 (3H, s), 0.92 (3H, s), 1.08–1.23 (4H, m), 1.35–1.69 (5H, m), 1.58 (3H, s), 1.77 (3H, s), 1.77–2.10 (7H, m), 4.13 (1H, d, $J = 7$ Hz), 5.36 (1H, t, $J = 7$ Hz). ^{13}C NMR: δ 19.1 (t), 19.1 (t), 19.6 (q), 20.2 (q), 21.7 (q), 23.4 (q), 27.0 (t), 32.9 (t), 33.3 (q), 33.3 (s), 33.6 (t), 37.0 (t), 39.0 (s), 41.8 (t), 51.8 (d), 59.3 (t), 123.7 (d), 126.3 (s), 140.2 (s), 140.9 (s). HREI-MS: *m*/*z*: calcd for $C_{20}H_{34}O$, 290.2610; found, 290.2611. (13*E*)-**16**: $[\alpha]_D^{25} = +67.8$ (*c* 1.11, $CHCl_3$); IR (neat): 3328, 1665 cm^{-1}; ^1H NMR: δ 0.81 (3H, s), 0.86 (3H, s), 0.92 (3H, s), 1.07–1.18 (3H, m), 1.32–1.48 (4H, m), 1.52–1.69 (2H, m), 1.55 (3H, s), 1.69 (3H, s), 1.80 (1H, br d, $J = 12.5$ Hz), 1.89–2.12 (6H, m), 4.14 (2H, d, $J = 7$ Hz), 5.41 (1H, br t, $J = 7$ Hz). ^{13}C NMR: δ 16.5 (q), 19.2 (t), 19.7 (t), 19.7 (t), 20.3 (q), 21.9 (q), 26.9 (t), 33.4 (s), 33.4 (q), 33.8 (t), 37.1 (t), 39.2 (s), 40.3 (t), 41.9 (t), 52.0 (d), 59.5 (t), 122.5 (d), 125.9 (s), 140.0 (s), 140.6 (s). Anal. Calcd for $C_{20}H_{34}O$: C, 82.69; H, 11.80. Found: C, 82.25; H, 11.80.

6.7. [8(9),5*S*,10*S*,13*E*]-Labdadien-15-al 12

To a solution of (13*E*)-**16** (0.284 g, 0.98 mol) in CH_2Cl_2 (10 mL) was added Dess–Martin periodinane (0.511 g, 1.2 mmol) at 0 °C and the mixture was stirred for 1 h at the same temperature. The reaction mixture was diluted with 7% aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and evaporated to give a residue, which was chromatographed on silica gel (5 g, *n*-hexane/AcOEt = 20:1) to give (10*S*,13*E*)-**12** (0.253 g, 89%) as a colourless oil. (10*S*,13*E*)-**12**: $[\alpha]_D^{23} = +66.9$ (*c* 1.08, $CHCl_3$); IR (neat): 1675, 1633 cm^{-1}; ^1H NMR: δ 0.81 (3H, s), 0.86 (3H, s), 0.92 (3H, s), 1.07–1.17 (2H, m), 1.32–1.65 (5H, m), 1.55 (3H, s), 1.77 (1H, br d, $J = 12.5$ Hz), 1.90–2.07 (4H, m), 2.12–2.27 (3H, m), 2.17 (3H, s), 5.88 (1H, dt, $J = 1$, 8 Hz), 9.97 (1H, d, $J = 8$ Hz). ^{13}C NMR: δ 17.8 (q), 19.2 (t), 19.2 (t), 19.6 (q), 20.3 (q), 21.8 (q), 26.1 (q), 33.4 (q), 33.4 (s), 33.7 (t), 37.1 (t), 39.2 (s), 41.4 (t), 41.8 (t), 51.9 (d), 126.6 (d), 126.8 (s), 139.0 (s), 164.3 (s), 191.0 (d). Anal. Calcd for $C_{20}H_{32}O$: C, 83.27; H, 11.18. Found: C, 82.87; H, 11.14.

6.8. (*R*)-3-Benzothiazolylsulfanyl-1-*tert*-butyldiphenylsilyloxy-2-methylpropane 13a

(i) To a solution of commercially available (*S*)-**17** (1.0 g, 8.5 mmol) in DMF (20 mL) was added *tert*-butyliphenylsilyl chloride (TBDPSCl, 2.74 g, 10 mmol) and imidazole (0.68 g, 10 mmol) at 0 °C and the whole mixture was stirred for 2 h at rt. The reaction mixture was diluted with brine and extracted with Et_2O. The organic layer was dried over $MgSO_4$ and evaporated to give a residue, which was chromatographed on silica gel (90 g, *n*-hexane/AcOEt = 50:1) to give the corresponding silyl ether **18** (2.739 g, 90%). (*S*)-Silyl ether **18**: $[\alpha]_D^{24} = +17.0$ (*c* 1.31, $CHCl_3$); ^1H NMR: δ 1.02 (9H, s), 1.14 (3H, d, $J = 7$ Hz), 2.67–2.72 (1H, m), 3.67 (3H, s), 3.71 (1H, dd, $J = 9.8$, 5.8 Hz), 3.81 (1H, dd, $J = 9.8$, 6.8 Hz), 7.34–7.43 (6H, m), 7.61–7.66 (4H, m). (ii) A mixture of silyl ether (2.685 g, 7.5 mmol) and $LiBH_4$ (0.804 g, 36 mmol) in THF (30 mL) was stirred for 6 h at 50 °C. To the reaction mixture was added acetone (5 mL) at 0 °C and the whole mixture was diluted with brine and extracted with Et_2O. The organic layer was dried over $MgSO_4$ and evaporated to give a residue, which was chromatographed on silica gel (60 g, *n*-hexane/AcOEt = 5:1) to give a colourless oil (*S*)-**19** (2.440 g, 98%). (*S*)-**19**: $[\alpha]_D^{25} = +5.2$ (*c* 1.0, $CHCl_3$); ^{13}C NMR: δ 13.3, 19.3, 27.0 (3C), 37.4, 67.6, 68.7, 127.6 (4C), 129.6 (2C), 133.0 (2C), 135.0, 135.4 (4C). (iii) To a solution of alcohol (1.0 g, 3.0 mmol) in THF (20 mL) was added Ph_3P (0.963 g, 3.7 mmol), 2-mercaptobenzothiazole (BTSH, 0.642 g, 3.8 mmol) and 2.2 M diethylazodicarboxylate in toluene solution (1.5 mL, 3.3 mmol) at 0 °C and the whole mixture was stirred for 1 h at rt. The reaction mixture was diluted with brine and extracted with Et_2O. The organic layer was dried over $MgSO_4$ and evaporated to give a residue, which was chromatographed on silica gel (50 g, *n*-hexane/AcOEt = 20:1) to give the corresponding sulfide **20a** (1.19 g, 82%) as a colourless oil. Sulfide **20a**: $[\alpha]_D^{22} = +7.3$ (*c* 1.05, $CHCl_3$); ^1H NMR: δ 1.44 (9H, s), 1.45 (3H, d, $J = 7.8$ Hz), 2.52–2.61 (1H, m), 3.64 (1H, dd, $J = 13$, 7 Hz), 3.95–4.02 (2H, m), 4.04–4.10 (1H, m), 7.61–7.81 (8H, m), 8.02–8.06 (4H, m), 8.10 (1H, dd, $J = 7.3$, 0.6 Hz), 8.20 (1H, dd, $J = 7.3$, 0.6 Hz). ^{13}C NMR: δ 16.5, 19.5, 27.0 (3C), 36.1, 37.2, 67.2, 120.7, 121.3, 123.9, 125.8, 127.5 (4C), 129.5 (2C), 133.4 (2C), 135.0, 135.4 (4C), 153.1, 167.3. Anal. Calcd for $C_{27}H_{31}NOS_2Si$: C, 67.88; H, 6.54; N, 2.93. Found: C, 67.38; H, 6.53; N, 2.86. FAB MS *m*/*z*: 478 (M^++1). (iv) To a solution of sulfide (**20a**, 1.21 g, 2.3 mmol) in EtOH (15 mL) was added $Mo_7O_{24}(NH_4)_6{\cdot}4H_2O$ (0.295 g, 0.24 mmol) and 30% H_2O_2 (1.8 mL) at 0 °C and the whole mixture was stirred for 4 h at room temperature. The reaction mixture was diluted with 10% aqueous $Na_2S_2O_3$ and extracted with Et_2O. The organic layer was washed with brine and dried over $MgSO_4$. The organic layer was evaporated to give a crude residue, which was chromatographed on silica gel (30 g, *n*-hexane/AcOEt = 10:1) to afford **13a** (0.959 g, 80%) as a colourless oil. Compound **13a**: $[\alpha]_D^{24} = +21.7$ (*c* 0.91, $CHCl_3$); ^1H NMR: δ 0.98 (9H, s), 1.11 (3H, d, $J = 6.8$ Hz), 2.39–2.50 (1H, m), 3.29 (1H, dd, $J = 14.5$, 8.6 Hz), 3.45 (1H, dd, $J = 10$, 7 Hz), 3.64 (1H, dd, $J = 10$, 5 Hz), 3.93 (1H, dd, $J = 14.5$, 4 Hz), 7.28–7.40 (6H, m), 7.53–7.63 (6H, m), 7.98–8.00 (1H, m), 8.16–8.19 (1H, m). ^{13}C NMR: δ 16.8, 19.3, 26.9 (3C), 31.7, 57.7, 67.1, 122.2, 125.4, 127.4, 127.5 (4C), 127.8, 129.6 (2C), 133.0 (2C), 135.3 (4C), 136.7, 152.5, 166.2. Anal. Calcd for $C_{27}H_{31}NO_3S_2Si$: C, 63.61; H, 6.13; N, 2.74. Found: C, 63.09; H, 6.31; N, 2.75. FAB MS *m*/*z*: 532 (M^++Na).

6.9. (*R*)-3-(1′-Phenyl-1′*H*-tetrazole-5′-sulfanyl)-1-*tert*-butyldiphenylsilyloxy-2-methylpropane 13b

(i) To a solution of alcohol (*S*)-**19** (1.15 g, 3.5 mmol) in THF (20 mL) was added Ph_3P (1.10 g, 4.2 mmol), 1-phenyl-1*H*-tetrazole-5-thiol (PTSH, 0.750 g, 4.2 mmol) and 2.2 M diethylazodicarboxylate in toluene solution (2 mL, 4.4 mmol) at 0 °C and whole mixture was stirred for 3 h at rt. The reaction mixture was diluted with 2 M aqueous NaOH and extracted with Et_2O. The organic layer was washed with brine and dried over $MgSO_4$. Evaporation of the organic solvent gave a residue, which was chromatographed on silica gel (50 g, *n*-hexane/AcOEt = 10:1) to afford the corresponding sulfide **20b** (1.64 g, 96%) as a colourless oil. Sulfide **20b**; $[\alpha]_D^{23} = -2.5$ (*c* 0.82, $CHCl_3$); ^{1}H NMR: δ 1.03 (9H, s), 1.06 (3H, d, $J = 6.8$ Hz), 2.15–2.23 (1H, m), 3.40–3.59 (3H, m), 3.67 (1H, dd, $J = 10.2$, 4.8 Hz), 7.31–7.42 (6H, m), 7.51–7.56 (5H, m), 7.61–7.65 (4H, m). ^{13}C NMR: δ 16.5, 19.4, 27.0 (3C), 35.6, 36.9, 67.0, 123.7 (2C), 127.5 (4C), 129.5 (2C), 129.6 (2C), 129.8, 133.2, 133.3, 133.6, 135.4 (4C), 154.5. Anal. Calcd for $C_{27}H_{32}N_4OSSi$: C, 66.35; H, 6.60; N, 11.46. Found: C, 6.30; H, 6.62; N, 11.33. FAB MS *m*/*z*: 489 (M^++1). (ii) To a solution of sulfide (1.23 g, 2.5 mmol) in EtOH (15 mL) was added $Mo_7O_{24}(NH_4)_6{\cdot}4H_2O$ (0.375 g, 0.3 mmol) and 30% H_2O_2 (1.8 mL) at 0 °C and the whole mixture was stirred for 4 h at room temperature. The reaction mixture was diluted with 10% aqueous $Na_2S_2O_3$ and extracted with Et_2O. The organic layer was washed with brine and dried over $MgSO_4$. The organic layer was evaporated to give a crude residue, which was chromatographed on silica gel (30 g, *n*-hexane/AcOEt = 15:1) to afford **13b** (0.774 g, 59%) as a colourless oil. Compound **13b**: $[\alpha]_D^{24} = +9.2$ (*c* 0.77, $CHCl_3$); ^{1}H NMR: δ 1.05 (9H, s), 1.14 (3H, d, $J = 6.8$ Hz), 2.46–2.55 (1H, m), 3.52 (1H, dd, $J = 10$, 6 Hz), 3.56 (1H, dd, $J = 14$, 8 Hz), 3.72 (1H, dd, $J = 10$, 5 Hz), 4.12 (1H, dd, $J = 10$, 5 Hz), 7.34–7.43 (6H, m), 7.61–7.67 (9H, m). ^{13}C NMR: δ 16.9, 19.4, 26.9 (3C), 31.3, 60.4, 67.0, 125.0 (2C), 127.7 (4C), 129.5 (2C),, 129.7 (2C), 131.3 (2C), 132.9 (2C), 135.4 (4C), 153.8. FAB MS *m*/*z*: 543 (M^++Na).

6.10. Modified Julia's coupling of (10*S*)-12 and 13a: synthesis of (18*S*,3*E*)-21

To a solution of (10*S*)-**12** (0.251 g, 0.87 mmol) and **13a** (0.460 g, 0.9 mmol) in THF (5 mL) was added lithium bis(trimethylisilyl)amide (1 M solution in THF, 1.8 mL, 1.8 mmol) at −78 °C under an argon atmosphere and the whole mixture was stirred for 1 h at the same temperature. The reaction mixture was diluted with brine and extracted with Et_2O. The organic layer was dried over $MgSO_4$. Evaporation of the organic solvent gave a crude product, which was chromatographed on silica gel (10 g, *n*-hexane/AcOEt = 50:1) to give a 6.2:1 (*E*:*Z*) mixture (0.372 g, 73%) of (3*E*)-**21** and (3*Z*)-**21** as a colourless oil. (3*E*)-**21** (major product); ^{1}H NMR: δ 0.82 (3H, s), 0.87 (3H, s), 0.93 (3H, s), 1.04 (9H, s), 1.04 (3H, d, $J = 6.8$ Hz), 1.08–1.87 (7H, m), 1.57 (3H, s), 1.74 (3H, s), 1.89–2.14 (6H, m), 2.39–2.47 (1H, m), 3.44–3.58 (2H, m), 5.47 (1H, dd, $J = 15$, 7 Hz), 5.78 (1H, d, $J = 11$ Hz), 6.24 (1H, dd, $J = 15$, 11 Hz), 7.33–7.41 (6H, m), 7.64–7.66 (4H, m). ^{13}C NMR: δ 15.4 (q), 16.8 (q), 17.0 (q), 19.3 (t), 19.5 (s), 19.7 (q), 20.3 (q), 21.9 (q), 27.0 (q, 3C), 27.1 (t), 33.8 (t), 37.1 (t), 39.2 (s), 39.8 (d), 40.7 (t), 41.9 (t), 52.0 (d), 60.4 (s), 65.9 (t), 68.8 (t), 119.4 (d), 124.0 (d), 124.8 (d), 125.8 (s), 126.3 (d), 127.4 (d, 4C), 129.3 (d), 132.2 (d), 133.9 (s), 134.3 (d), 135.5 (d, 2C), 137.8 (s), 139.7 (s), 140.2 (s). FAB MS *m*/*z*: 583 (M^++1).

6.11. Modified Julia's coupling of (10*S*)-12 and 13b: synthesis of (18*S*,3*E*)-21

To a solution of (10*S*)-**12** (0.225 g, 0.78 mmol) and **13b** (0.371 g, 0.71 mmol) in THF (5 ml) was added lithium bis(trimethylisilyl)amide (1 M solution in THF, 1.5 mL, 1.5 mmol) at −78 °C under an argon atmosphere and the whole mixture was stirred for 3 h at the same temperature. The reaction mixture was diluted with brine and extracted with Et_2O. The organic layer was dried over $MgSO_4$. Evaporation of the organic solvent gave a crude product, which was chromatographed on silica gel (10 g, *n*-hexane/AcOEt = 50:1) to give a 11:1 (*E*:*Z*) mixture (0.376 g, 83%) of (3*E*)-**21** and (3*Z*)-**21** as a colourless oil.

6.12. Norsesterterpene diene alcohol (18*S*,3*E*)-22

To a solution of (18*S*,3*E*)-**21** (0.375 g, 0.64 mmol) in THF (5 mL) was added 1 M tetrabutylammonium fluoride (TBAF) THF solution (1 mL, 1 mmol) at rt, and the whole mixture was stirred for 1 h at the same temperature. The reaction mixture was diluted with brine and extracted with Et_2O. The organic layer was dried over $MgSO_4$. Evaporation of the organic solvent gave a crude product, which was chromatographed on silica gel (10 g, *n*-hexane/AcOEt = 10:1) to give (18*S*,3*E*)-**22** (0.185 g, 81%) as a colourless oil. (18*S*,3*E*)-**22**: $[\alpha]_D^{24} = +82.6$ (*c* 0.65, $CHCl_3$); IR (neat): 3361 cm^{-1}; ^{1}H NMR: δ 0.81 (3H, s), 0.86 (3H, s), 0.92 (3H, s), 1.01 (3H, d, $J = 6.8$ Hz), 1.05–1.84 (9H, m), 1.56 (3H, s), 1.77 (3H, s), 2.38–2.45 (1H, m), 3.39 (1H, dd, $J = 10$, 8 Hz), 3.50 (1H, dd, $J = 10$, 6 Hz), 5.41 (1H, d, $J = 15$, 8 Hz), 5.82 (1H, d, $J = 11$ Hz), 6.33 (1H, dd, $J = 15$, 11 Hz). ^{13}C NMR: δ 16.6 (q), 16.7 (q), 19.1 (t), 19.5 (t), 20.1 (t), 21.7 (q), 26.8 (t), 33.3 (s), 33.3 (q), 33.6 (t), 37.0 (t), 39.1 (s), 40.1 (d), 40.5 (t), 41.8 (t), 51.9 (d), 67.4 (t), 123.6 (d), 126.0 (s), 128.0 (d), 133.6 (d), 139.0 (s), 140.2 (s). HREI-MS: calcd for $C_{24}H_{40}O$, 344.3080; found, 344.3068.

6.13. (+)-Norsesterterpene diene ester 2

(i) A mixture of (18*S*,3*E*)-**22** (0.135 g, 0.39 mmol) and Dess–Martin reagent (0.198 g, 0.47 mmol) in CH_2Cl_2 (3 mL) was stirred at 0 °C and the reaction mixture was stirred for 30 min. The reaction mixture was diluted with 10% aqueous Na_2CO_3 and extracted with Et_2O. The organic layer was washed with brine and dried over $MgSO_4$. Evaporation of the organic solvent gave a residue, which was chromatographed on silica gel (15 g, *n*-hexane/AcOEt = 20:1) to afford aldehyde **23** (0.072 g, 53%). Compound **23**: $[\alpha]_D^{26} = -44.3$ (*c* 0.78, $CHCl_3$); IR (KBr): 1696 cm^{-1}; ^{1}H NMR: δ 0.81 (3H, s), 0.86 (3H, s), 0.92 (3H, s), 1.21 (3H, d, $J = 6.9$ Hz), 1.05–1.86 (15H, m), 1.56 (3H, s), 1.78 (3H, s), 5.48 (1H, d, $J = 15$, 8 Hz), 5.85

(1H, d, $J = 11$ Hz), 6.30 (1H, d, $J = 15$, 11 Hz), 9.50 (1H, d, $J = 1.6$ Hz). ^{13}C NMR: δ 13.8 (q), 17.0 (q), 19.2 (t, 2C), 19.7 (q), 20.3 (q), 21.9 (q), 27.0 (t), 33.4 (q), 33.5 (s), 33.8 (t), 37.1 (t), 39.2 (s), 40.6 (t), 41.9 (t), 50.4 (d), 52.0 (d), 123.2 (d), 126.0 (s), 126.3 (d), 130.1 (d), 139.9 (s), 140.5 (s), 201.2 (s). HREI-MS: calcd for $C_{24}H_{38}O$, 342.2913; found, 342.2918. (ii) To a solution of (18*S*,3*E*)-**23** (0.053 g, 0.15 mmol) and 2-methyl-2-butene (6 mL) in *tert*-BuOH (2 mL) was added $NaClO_2$ (0.144 g, 1.6 mmol) and NaH_2PO_4 (0.115 g, 0.96 mmol) in H_2O (0.5 mL) at rt and the whole mixture was stirred for 30 min at the same temperature. The reaction mixture was diluted with 2 M aqueous HCl and extracted with Et_2O. The organic layer was dried over $MgSO_4$. Evaporation of the organic solvent gave a crude product, which was chromatographed on silica gel (5 g, *n*-hexane/AcOEt = 3:1) to give a carboxylic acid (**24**, 0.055 g, quantitative yield) as a colourless oil. (18*S*,3*E*)-**24**. IR (KBr): 3420, 1696 cm^{-1}; HREI-MS: calcd for $C_{24}H_{38}O_2$, 358.2872; found, 358.2888. (iii) This acid **24** was treated with CH_2N_2–ether solution to give a crude oil, which was chromatographed on silica gel (10 g, *n*-hexane/AcOEt = 50:1) to afford (+)-(18*S*,3*E*)-**2** (0.019 g, 33%) as a colourless oil. (+)-(18*S*,3*E*)-**2**: $[\alpha]_D^{25} = +12.4$ (*c* 0.55, $CHCl_3$); ^{1}H NMR: δ 0.82 (3H, s), 0.88 (3H, s), 0.94 (3H, s), 1.12 (1H, dd, $J = 12.5$, 2 Hz), 1.12–1.20 (2H, m), 1.29 (3H, d, $J = 7$ Hz), 1.34–1.67 (5H, m), 1.57 (3H, s), 1.78 (3H, d, $J = 1$ Hz), 1.80–1.85 (1H, m), 1.91–2.13 (6H, m), 3.20 (1H, ddq, $J = 1$, 7, 8 Hz), 3.68 (3H, s), 5.63 (1H, dd, $J = 15$, 8 Hz), 5.84 (1H, d, $J = 11$ Hz), 6.34 (1H, ddd, $J = 15$, 11, 1 Hz). ^{13}C NMR: δ 16.9, 17.6, 19.2 (2C), 19.7, 20.2, 21.8, 26.9, 33.4 (2C), 33.7, 37.1, 39.1, 40.6, 41.9, 43.2, 51.9, 52.0, 123.2, 125.9, 127.8, 129.5, 140.0 (2C), 175.0.

6.14. 14,15-Bisnor-[8(9),5*R*,10*R*]-labdaen-13-one 14

(5*R*,10*R*)-Methyl ketone **14** was synthesized from (8a*R*)-**7** in 37% overall yield in the same way as for preparation of (5*S*,10*S*)-**14** from (8a*S*)-**7**. (5*R*,10*R*)-**14**: $[\alpha]_D^{24} = -82.0$ (*c* 1.11, $CHCl_3$). ^{1}H NMR spectra of (5*R*,10*R*)-**14** were identical with those of (5*S*,10*S*)-**14**.

6.15. [8(9),5*S*,10*R*,13*E*]-Labdadien-15-ol 16

(10*R*,13*E*)-Allyl alcohol **16** was synthesized from (5*R*,10*R*)-**14** in 45% overall yield in the same way as for preparation of (10*S*,13*E*)-**16** from (5*S*,10*S*)-**14**. (10*R*,13*E*)-**16**: $[\alpha]_D^{25} = -71.2$ (*c* 1.11, $CHCl_3$). ^{1}H NMR spectra of (10*R*,13*E*)-**16** were identical with those of (10*S*,13*E*)-**16**.

6.16. Tetrahydropyranyloxy derivative of (3-tributhylstannyl-4-methoxymethoxyphenyl)methanol

To a solution of the known aryl bromide congener **27**[11] (0.694 g, 2.1 mmol) in THF (30 mL) was added 1.6 M *tert*-BuLi in pentane solution (2.7 mL, 4.4 mmol) at −78 °C and the mixture was stirred for 1 h at −78 °C. Tributyltin chloride (*n*-Bu_3SnCl 1.77 g, 5.43 mmol) was added to the above mixture solution at −78 °C and whole mixture was stirred for 1 h at −78 °C. The reaction mixture was evaporated to a residue, which was diluted with H_2O and extracted with AcOEt. The organic layer was washed with brine and dried over $MgSO_4$. Evaporation of the organic solvent gave a residue, which was chromatographed on Florisil (20 g, *n*-hexane/AcOEt = 100:1) to afford **26** (0.698 g, 62%) as a colourless oil. **26**; IR (neat): 1156 cm^{-1}; ^{1}H NMR: δ 0.86 (9H, t, $J = 7.3$ Hz), 0.96–1.08 (8H, m), 1.26–1.35 (6H, m), 1.48–1.75 (9H, m), 1.80–1.89 (1H, m), 3.44 (3H, s), 3.51–3.56 (1H, m), 3.90–3.95 (1H, m), 4.42 (1H, d, $J = 11.4$ Hz), 4.68–4.69 (1H, m), 4.71 (1H, d, $J = 11.4$ Hz), 5.13 (2H, s), 7.02 (1H, d, $J = 8.5$ Hz), 7.27 (1H, dd, $J = 8.5$, 2.2 Hz), 7.34 (1H, d, $J = 2.2$ Hz). ^{13}C NMR: δ 10.0 (t, 3C), 13.9 (q, 3C), 19.6 (t), 25.7 (t), 27.2 (t), 27.5 (t), 27.8 (t), 29.2 (t), 29.3 (t), 29.4 (t), 30.7 (t), 55.8 (q), 62.3 (t), 68.7 (t), 94.1 (t), 97.5 (d), 111.7 (d), 129.7 (d), 130.4 (s), 131.1 (s), 136.8 (d), 161.1 (s). Anal. Calcd for $C_{26}H_{46}O_4Sn$: C, 57.68; H, 8.56. Found: C, 57.48; H, 8.86. MALDI-TOF-MS *m*/*z*: 541 (M^+).

6.17. Reaction of aryl stannane 26 and (10*R*,13*E*)-carbonate 25b

(i) A mixture of (10*S*,13*E*)-**16** (0.195 g, 0.67 mmol) and ethyl chloroformate (0.364 g, 3.5 mmol) in pyridine (5 mL) was stirred at 0 °C and the reaction mixture was stirred for 1 h. The reaction mixture was diluted with 7% aqueous $NaHCO_3$ and extracted with Et_2O. The organic layer was washed with 2 M aqueous HCl and brine and dried over $MgSO_4$. Evaporation of the organic solvent gave a residue, which was chromatographed on silica gel (10 g, *n*-hexane/AcOEt = 100:1) to afford a carbonate **25b** (0.217 g, 82%) as a colourless oil. Compound **25b**: $[\alpha]_D^{25} = -65.1$ (*c* 1.05, $CHCl_3$); IR (neat): 1744 cm^{-1}; ^{1}H NMR: δ 0.81 (3H, s), 0.86 (3H, s), 0.91 (3H, s), 1.07–1.22 (3H, m), 1.28 (3H, t, $J = 7$ Hz), 1.35–1.48 (3H, m), 1.52–1.64 (2H, m), 1.55 (3H, s), 1.72 (3H, d, $J = 0.5$ Hz), 1.75–1.82 (1H, m), 1.88–2.12 (6H, m), 4.17 (2H, dd, $J = 14$, 7 Hz), 4.62 (2H, d, $J = 7$ Hz), 5.37 (1H, dt, $J = 7$, 0.5 Hz). ^{13}C NMR: δ 14.4 (q), 16.7 (q), 19.2 (t, 2C), 19.6 (q), 20.2 (q), 21.8 (q), 26.7 (t), 33.4 (q), 33.4 (q), 33.8 (t), 33.7 (t), 39.1 (s), 40.2 (t), 41.9 (t), 52.0 (d), 63.8 (t), 64.6 (t), 117.0 (d), 126.0 (s), 139.8 (s), 143.8 (s), 155.0 (s). EI-MS: *m*/*z* 362 (M^+) (ii) To a solution of **25b** (0.217 g, 0.60 mmol) in DMF (20 mL) was added **26** (0.659 g, 1.2 mmol), tris(dibenzylideneacetone)dipalladium(0)-chloroform adduct [$Pd_2(dba)_3{\cdot}CHCl_3$, 0.037 g, 0.036 mmol] and LiCl (0.085 g, 2 mmol) and the reaction mixture was stirred for 4 h at 100 °C. The reaction mixture was diluted with H_2O and extracted with Et_2O. The organic layer was washed with brine and dried over $MgSO_4$. Evaporation of the organic solvent gave a crude oil, which was chromatographed on silica gel (25 g, *n*-hexane/AcOEt = 100:1) to afford a mixture (0.400 g) of **26** and **28**. (iii) To a solution of the above mixture in MeOH (10 mL) was added *p*-TsOH (0.309 g, 1.79 mmol) and the reaction mixture was stirred for 2 h at rt. The reaction mixture was diluted with H_2O (5 mL) and evaporated under reduced pressure to give a residue. This residue was diluted with H_2O and extracted with Et_2O. The organic layer was washed with brine and dried over $MgSO_4$. Evaporation of the organic solvent gave a crude oil, which was chromatographed on silica gel (15 g, *n*-hexane/AcOEt = 5:1) to afford a 1:1 mixture (0.117 g, 44% overall yield from (13*E*)-**16**) of (2′*E*)-**29** and (2′*Z*)-**29**. The *E*/*Z* ratio was calculated based on the NMR ana-

lysis of integrated values due to the olefinic proton (δ 5.30 (t) and 5.24 (t)). Physical data of the desired (2′*E*)-**29** is shown in Section 6.19.

6.18. Reaction of aryl stannane 26 and (10*R*,13*E*)-trifluoroacetate 25c

(i) To a solution of (10*S*,13*E*)-**16** (0.204 g, 0.7 mmol) and in CH_2Cl_2 (5 mL) was added 2,6-lutidine (0.232 g, 2.2 mmol) and trifluoroacetic anhydride (TFAA, 0.252 g, 1.2 mmol) at −78 °C and the reaction mixture was stirred for 2 h at the same temperature. The reaction mixture was diluted with H_2O at 0 °C and extracted with CH_2Cl_2. The organic layer was washed with 7% aqueous $NaHCO_3$ and dried over $MgSO_4$. Evaporation of the organic solvent gave a crude **25c** (0.287 g, quantitative yield), which was used for the next reaction without further purification. Compound **25c**: $[\alpha]_D^{23} = -55.7$ (*c* 1.14, $CHCl_3$); IR (neat): 1784 cm^{-1}; ^1H NMR: δ 0.82 (3H, s), 0.87 (3H, s), 0.92 (3H, s), 1.09–1.21 (3H, m), 1.38–1.65 (5H, m), 1.58 (3H, s), 1.61–1.76 (1H, m), 1.55 (3H, s), 1.82 (3H, d, $J = 0.5$ Hz), 1.91–2.17 (6H, m), 4.82 (2H, d, $J = 7$ Hz), 5.36 (1H, dt, $J = 7$, 0.5 Hz). ^{13}C NMR: δ 16.6 (q), 19.1 (t, 2C), 19.5 (q), 20.1 (q), 21.7 (q), 26.5 (t), 33.3 (q), 33.3 (s), 33.6 (t), 37.0 (t), 39.1 (s), 40.2 (t), 41.8 (t), 51.9 (d), 64.9 (t), 115.2 (d), 126.3 (s), 139.8 (s), 146.6 (s), 157.3 (s), 157.8 (s). HREI-MS: calcd for $C_{22}F_3H_{33}O_2$, 386.2433; found, 386.2447. (ii) To a solution of **25c** (0.287 g) in DMF (3 mL) was added **26** (0.495 g, 0.92 mmol), $Pd_2(dba)_3{\cdot}CHCl_3$ (0.041 g, 0.04 mmol) and CuI (0.008 g, 0.04 mmol) and the reaction mixture was stirred for 24 h at rt. The reaction mixture was diluted with H_2O and extracted with AcOEt. The organic layer was washed with brine and dried over $MgSO_4$. Evaporation of the organic solvent gave a crude oil, which was chromatographed on silica gel (30 g, *n*-hexane/AcOEt = 80:1) to afford a mixture (0.242 g) of **26** and **28**. (iii) To a solution of the above mixture in MeOH (5 mL) was added pyridinium *p*-toluenesulfonate (PPTS, 0.105 g, 0.4 mmol) and the reaction mixture was stirred for 8 h at rt. The reaction mixture was diluted with H_2O and extracted with Et_2O. The organic layer was washed with 7% aqueous $NaHCO_3$ and dried over $MgSO_4$. Evaporation of the organic solvent gave a crude oil, which was chromatographed on silica gel (25 g, *n*-hexane/AcOEt = 10:1) to afford a 7:1 mixture [0.168 g, 54% overall yield from (13*E*)-**16**] of (2′*E*)-**29** and (2′*Z*)-**29**. The *E*/*Z* ratio was calculated based on the NMR analysis of integrated values due to the olefinic proton (δ 5.30 (t) and 5.24 (t)). (2′*E*)-**29** (major product): IR (neat): 3382 cm^{-1}; ^1H NMR: δ 0.81 (3H, s), 0.86 (3H, s), 0.91 (3H, s), 1.07–1.16 (2H, m), 1.35–1.46 (3H, m), 1.55 (3H, s), 1.58–1.64 (3H, m), 1.73 (3H, s), 1.75–1.81 (1H, m), 1.88–2.12 (6H, m), 3.33 (2H, d, $J = 7$ Hz), 3.45 (3H, s), 4.58 (2H, s), 5.18 (2H, s), 5.29 (1H, t, $J = 7$ Hz), 7.02 (1H, d, $J = 8$ Hz), 7.13 (1H, dd, $J = 8$, 2 Hz), 7.14 (1H, d, $J = 2$ Hz), 9.85 (1H, s). ^{13}C NMR: δ 16.2 (q), 19.1 (t, 2C), 19.6 (q), 20.2 (q), 21.7 (q), 28.6 (t), 29.3 (t), 33.3 (s), 33.3 (q), 33.6 (t), 37.0 (t), 39.0 (s), 40.5 (t), 41.8 (t), 51.9 (d), 55.9 (q), 65.2 (t), 94.2 (t), 113.9 (d), 121.6 (d), 125.7 (s), 125.8 (d), 128.7 (d), 128.8 (d), 131.1 (s), 134.0 (s), 137.1 (s), 140.5 (s), 154.4 (s). HREI-MS: calcd for $C_{29}H_{44}O_3$, 440.3291; found, 440.3296.

6.19. Oxidation of (2′*E*)-29 and (2′*Z*)-29

To a solution of a 7:1 mixture (0.113 g, 0.25 mmol) of (2′*E*)-**29** and (2′*Z*)-**29** and in CH_2Cl_2 (2 mL) was added MnO_2 (0.764 g, 8.8 mmol) at rt and the whole mixture was stirred for 2 h at the same temperature. The reaction mixture was filtered with the aid of Celite. The filtrate was evaporated to give a crude residue, which was chromatographed on silica gel (5 g, *n*-hexane/AcOEt = 50:1) to give an 8:1 mixture (0.104 g, 92%) of (2′*E*)-**30** and (2′*Z*)-**30** as a colourless oil. (2′*E*)-**30** (major product): IR (neat): 1692 cm^{-1}; ^1H NMR: δ 0.81 (3H, s), 0.86 (3H, s), 0.92 (3H, s), 1.10–1.18 (2H, m), 1.35–1.47 (3H, m), 1.52–1.64 (3H, m), 1.55 (3H, s), 1.74 (3H, s), 1.78–1.83 (1H, m), 1.81–2.11 (6H, m), 3.36 (2H, d, $J = 7$ Hz), 3.47 (3H, s), 5.27 (2H, s), 5.30 (1H, t, $J = 7$ Hz), 7.15 (1H, d, $J = 8$ Hz), 7.68 (1H, dd, $J = 8$, 2 Hz), 7.69 (1H, d, $J = 2$ Hz), 9.85 (1H, s). ^{13}C NMR: δ 16.4 (q), 19.2 (t, 2C), 19.7 (q), 20.3 (q), 21.8 (q), 27.3 (t), 28.7 (t), 33.4 (s), 33.4 (q), 33.7 (t), 37.1 (t), 39.1 (s), 40.6 (t), 41.9 (t), 52.0 (d), 56.3 (q), 93.9 (t), 113.1 (d), 120.5 (d), 125.7 (s), 130.0 (d), 130.3 (s, 2C), 130.8 (d), 131.4 (s), 137.9 (s), 140.2 (s), 191.0 (d). Anal. Calcd for $C_{29}H_{42}O_3{\cdot}H_2O$: C, 76.55; H, 9.42. Found: C, 76.27; H, 9.71. EI-MS *m*/*z*: 438 (M^+).

6.20. (−)-Subersic acid 3

(i) To a solution of a 8:1 mixture (0.122 g, 0.28 mmol) of (2′*E*)-**30** and (2′*Z*)-**30** and 2-methyl-2-butene (4 mL) in *tert*-BuOH (2 mL) was added $NaClO_2$ (0.263 g, 2.9 mmol) and NaH_2PO_4 (0.212 g, 1.8 mmol) in H_2O (1 mL) at rt and the whole mixture was stirred for 3 h at the same temperature. The reaction mixture was diluted with 2 M aqueous HCl and extracted with Et_2O. The organic layer was dried over $MgSO_4$. Evaporation of the organic solvent gave a crude product, which was chromatographed on silica gel (5 g, *n*-hexane/AcOEt = 10:1) to give a 9:1 mixture (0.068 g, 53%) of (2′*E*)-**31** and (2′*Z*)-**31** as a colourless oil. Major (2′*E*)-**31**: IR (neat): 1686 cm^{-1}; ^1H NMR: δ 0.81 (3H, s), 0.86 (3H, s), 0.92 (3H, s), 1.08–1.20 (2H, m), 1.33–1.48 (3H, m), 1.52–1.59 (3H, m), 1.55 (3H, s), 1.74 (3H, s), 1.78–1.83 (1H, m), 1.88–2.14 (6H, m), 3.35 (2H, d, $J = 7$ Hz), 3.46 (3H, s), 5.26 (2H, s), 5.30 (1H, t, $J = 7$ Hz), 7.08 (1H, d, $J = 8$ Hz), 7.90 (1H, d, $J = 2.3$ Hz), 7.91 (1H, dd, $J = 8$, 2.3 Hz). ^{13}C NMR: δ 16.4 (q), 19.2 (t, 2C), 19.7 (q), 20.2 (q), 21.9 (q), 27.3 (t), 28.7 (t), 33.4 (s), 33.5 (q), 33.7 (t), 37.1 (t), 39.1 (s), 40.6 (t), 41.9 (t), 52.0 (d), 56.2 (q), 93.9 (t), 112.7 (d), 120.9 (d), 121.1 (s), 125.7 (s), 129.8 (s), 130.7 (s), 131.7 (d), 137.6 (s), 140.3 (s), 159.1 (s), 171.0 (s). HREI-MS: calcd for $C_{29}H_{42}O_4$, 454.3078; found, 454.3083. (ii) To a solution of a 9:1 mixture (0.063 g, 0.14 mmol) of (2′*E*)-**31** and (2′*Z*)-**31** in THF (5 mL) was added 6 M aqueous HCl (3 mL) at rt and the whole mixture was stirred for 3 h at 40 °C. The reaction mixture was diluted with H_2O and extracted with AcOEt. The organic layer was washed with brine and dried over $MgSO_4$. Evaporation of the organic solvent gave a crude product, which was chromatographed on silica gel (15 g, *n*-hexane/AcOEt = 1:1) to give a carboxylic acid. This crude carboxylic acid was subjected to preparative HPLC to afford (−)-**3** (0.040 g, 69%) as a colourless amorphous solid. Compound (−)-**3**: $[\alpha]_D^{24} = -46.7$

(c 0.17, $CHCl_3$); IR (neat): 3280 (br), 1682, 1600 cm^{-1}; ^1H NMR: δ 0.81 (3H, s), 0.86 (3H, s), 0.92 (3H, s), 1.08–1.26 (3H, m), 1.32–1.48 (3H, m), 1.53–1.64 (3H, m), 1.55 (3H, s), 1.80 (3H, s), 1.88–2.12 (6H, m), 3.40 (2H, d, $J = 7$ Hz), 5.33 (1H, t, $J = 7$ Hz), 6.84 (1H, d, $J = 9$ Hz), 7.88 (1H, dd, $J = 9$, 1.8 Hz), 7.89 (1H, d, $J = 1.8$ Hz). ^{13}C NMR: δ 16.5 (q), 19.2 (t, 2C), 19.7 (q), 20.3 (q), 21.8 (q), 27.2 (t), 29.7 (t), 29.8 (t), 33.4 (q), 33.7 (t), 37.1 (t), 39.1 (s), 40.5 (t), 41.9 (t), 51.9 (d), 113.6 (d), 120.0 (d), 121.5 (s), 125.9 (s), 126.7 (s), 130.4 (d), 132.4 (d), 139.9 (s), 140.4 (s), 159.3 (s), 171.6 (s). Anal. Calcd for $C_{27}H_{38}O_3 \cdot 2H_2O$: C, 72.61; H, 9.48. Found: C, 72.88; H, 9.22. EI-MS m/z: 410 (M^+).

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