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Synthetic Studies on Prehispanolone and 14,15-Dihydroprehispanolone[1]

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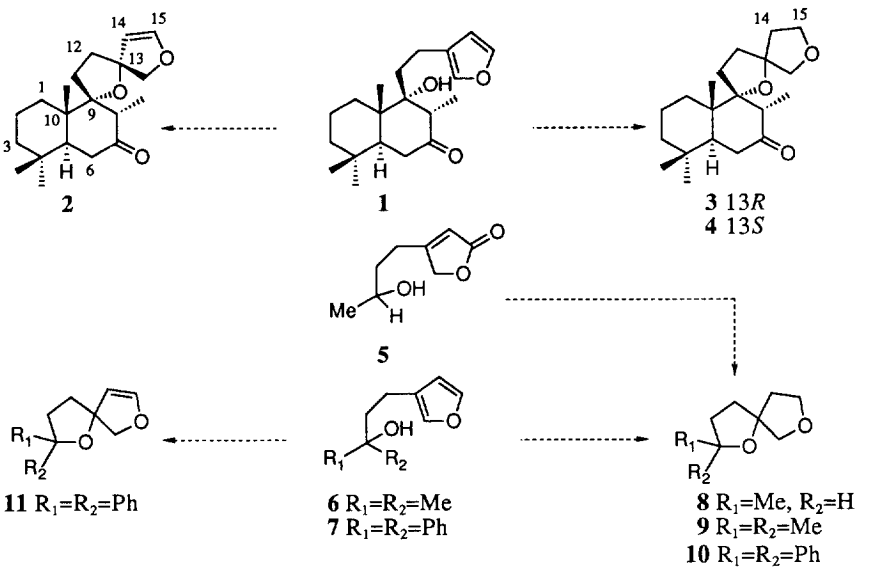
Abstract: Employing an intramolecular Michael addition as a pivotal step, butenolide **5**, furans **6** and **7** have been converted to dioxaspiro compounds **8**, **9**, **10** and **11**, whose heterocyclic frameworks constitute important structural units of prehispanolone (**2**) as well as 14,15-dihydroprehispanolones (**3**) and (**4**), respectively. Hispanolone (**1**) was converted to **2**, **3** and **4** by utilizing a similar strategy.

Hispanolone (**1**) was obtained from *Ballota hispanica* for the first time in 1978.[3] The transformation of **1** into its 8β–acetoxy counterpart, galeopsin, has been reported, together with its retro-aldol reaction in addition to other B ring transformations.[4] Preparation of drimane derivatives by using **1** as a precursor have also been reported.[5] The conversions of **1** to a perfumery substance, ambreinolide and to drimane sesquiterpenoids have also been described recently.[6] We recently reported the identification of labdane diterpene, namely prehispanolone (**2**) from the aerial parts of *Leonurus heterophyllus* (Yi Mu Cao).[1d] It was found that **2** can be converted readily to **1** by mild acid treatment,[1d,7] and indeed **1** become the sole product if neutral condition was not rigorously maintained during the isolation. Using an *in vitro* radioligand binding assay for the platelet activating factor (PAF) receptor,[8] compound **2** was identified as a specific PAF receptor antagonist.[1c] In remarkable contrast, **1**, which has been deprived of the tetrahydrofuran ring, did not interact with the PAF receptor.[1c] Catalytic hydrogenation of **2** converted it to the bioactive and acid-insensitive 14,15-dihydroprehispanolone (**3**).[1c,1d] Interestingly, in addition to being more acid-resistant than **2**, compound **3** was a much better ligand for PAF receptor.[1c] For further pharmacological evaluation purpose, it appears that both **2** and **3** are good leads for a structure-activity relationship study.

In view of the structural simplicity as well as the ready availability of 1, as compared with those of 2 and 3, we reason that 1 can serve as a pivotal intermediate *en route* to the total synthesis of 2 and 3. In order to assess such possibility, we also initiated a synthetic program with the aim to construct several model compounds, namely **5**, **6**, **7**, **8**, **9**, **10** and **11**. As can be seen, compounds **6** and **7** contain the functional characteristics of those of **1**, so they are able to allow the substantiation of our aforementioned argument.

Butenolide **5**, on the other hand, serves as an anchor molecule for our key intramolecular Michael cyclization step (*vide infra*), leading eventually to **8**. While **6** would be the precursor of **9**, we thought that the possible lower-boiling properties of **8** and **9** would cause a minor work-up problem. In this connection, we have also prepared the diphenyl analog **7** for the realization of **10** and **11**.

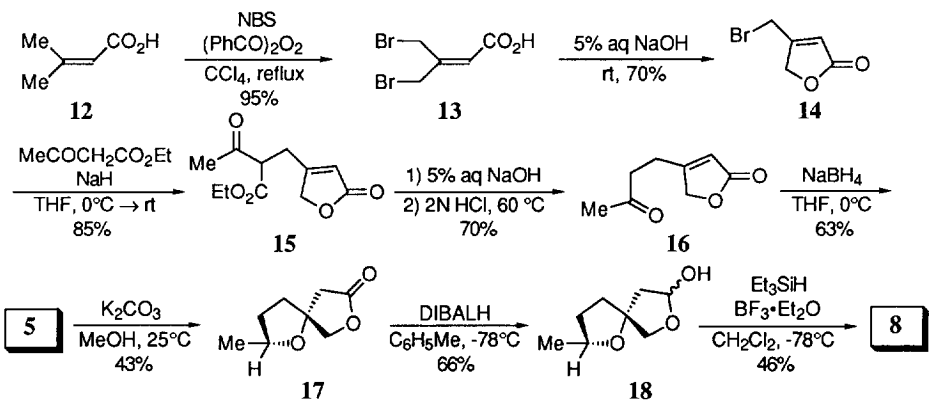
Scheme 1.



Synthesis of Model Compounds

To our best knowledge, no arduous attempt to construct dioxaspiro[4.4]nonane framework[9] similar to that of **2**, **3** and **4** has been reported, notwithstanding that such spiro moiety is a common structural unit in many natural products.[7,10] Our preliminary strategy employed for the synthesis of **8** was based on the intramolecular Michael addition of **5**. In order to examine the feasibility of this reaction, we elaborated a shorter route to synthesize the model molecule **8** from commercially available 3,3-dimethylacrylic acid (**12**) (Scheme 2).

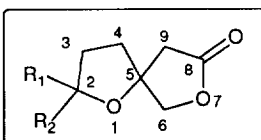
Scheme 2.



As outlined in Scheme 2, the synthesis of **5** from **12** was straightforward.[11-14] An intramolecular Michael addition of **5** gave **17** as a mixture of diastereomers.[15] The structure of the diastereomeric lactone **17** was confirmed by examining the ^{1}H NMR (Table 1) and ^{13}C NMR (Table 2) spectra of one of its diastereomers, as well as by its IR, MS and elemental analysis (see Experimental Section). Finally, **17** was converted[16] via the diasteromeric **18** to give **8** also as a diastereomeric mixture. As expected, the ^{1}H NMR spectrum of **8** showed the characteristic upfield shift for H-8 (δ 3.90) of **8** as compared with H-8 (δ 5.45) of the corresponding lactol **18**. Tables 3 and 4 summarize the assignments of the proton and C-13 absorptions of spiroethers **8**, **9**, **10** and **11**, respectively (assignments of only one diastereomer are shown in the case of diastereomeric mixtures).

Table 1. ^{1}H NMR data of compounds **17**, **42** and **43** in $CDCl_3$ [δ value from interal TMS, *J*, (Hz) in parentheses]

H	**17** (**A** isomer)	**42**	**43**
2	4.09 m		
3	2.05 m	2.08 t (6.7)	2.70 t (5.5)
4	1.55 m	1.83 t (6.7)	2.11 t (5.5)
6a	4.14 dd (10.0)	4.13 d (9.5)	4.14 d (9.6)
6b	4.32 dd (10.0)	4.23 d (9.5)	4.39 d (9.6)
9a	2.54 dd (17.7)	2.49 d (17.4)	2.54 d (17.4)
9b	2.77 dd (17.5)	2.69 d (17.4)	2.88 d (17.4)



17 R_1=Me, R_2=H
42 R_1= R_2=Me
43 R_1= R_2=Ph

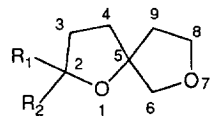
Table 2. ^{13}C NMR data of compounds **17**, **42** and **43** in $CDCl_3$

C	**17**[a]	**42**	**43**
2	75.4	82.0	89.4
3	34.0	38.8	38.4
4	33.2	34.8	35.0
5	84.5	84.8	85.4
6	77.6	78.1	77.8
8	174.3	174.3	174.7
9	41.3	41.7	41.3

[a] in C_6D_6

Table 3. ^{1}H NMR data of compounds **8**, **9**, **10** and **11** in $CDCl_3$ [δ value from interal TMS, *J*, (Hz) in parentheses]

H	**8** (**A** isomer)	**9**	**10**	**11**
2	4.10 m			
3	1.95 m	1.84 m	2.25 m	1.64 t (7.0)
4	2.12 m	1.77 m	2.05 m	2.11 m
6a	3.54 d (9.0)	3.58 d (8.8)	3.62 d (9.0)	4.00 d (10.05)
6b	3.76 d (9.0)	3.60 d (8.8)	3.92 d (9.0)	4.33 d (10.05)
8	3.90 m	3.86 m	4.02 t (7.5)	6.55 d (2.6)
9	2.05 m	2.01 m	2.65 t (7.5)	5.09 d (2.6)



8 R_1=Me, R_2=H
9 R_1= R_2=Me
10 R_1= R_2=Ph
11 R_1= R_2=Ph,
C_8, C_9=-CH=CH-

Table 4. ^{13}C NMR data of compounds **9**, **10** and **11** in $CDCl_3$

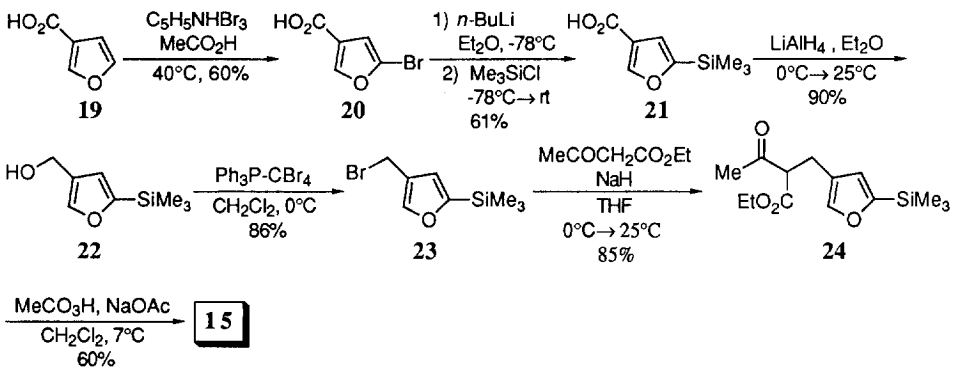
C	**9**[a]	**10**	**11**
2	89.4	90.1	92.3
3	40.6	39.6	39.2
4	39.1	39.2	36.8
5	80.7	88.4	88.2
6	67.8	67.9	80.5
8	78.6	77.5	149.1
9	35.8	34.9	106.2

[a] in C_6D_6

Despite the successful synthesis of spiroether **8**, the route shown in Scheme 2 is not suitable for natural **1**. In our particular case, we were guided by the desire to develop a method which would deliver a butenolide moiety from a furan functionality, thereby facilitating the realization of **2** directly from **1**.

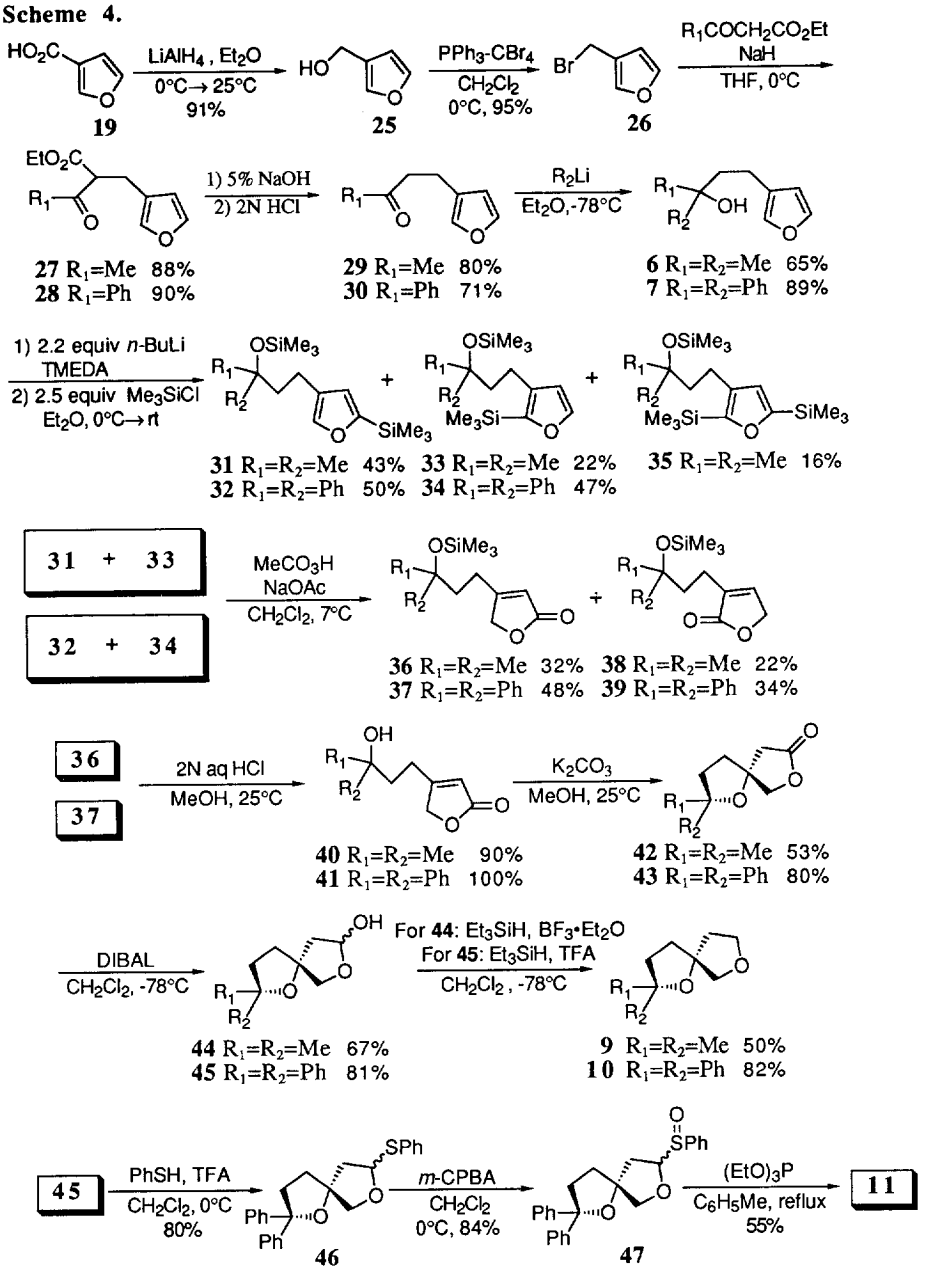
Our synthetic pathway therefore called for the direct introduction of the trimethylsilyl group to C-15 position of hispanolone (**1**) in a regioselective manner. If this regioselective method indeed works, our strategy would provide a convenient new pathway to the spiroether diterpenes. In order to examine the feasibility of such strategy, we elaborated a route to synthesize the model molecule **8** from commercially available 3-furancarboxylic acid (**19**). As shown in Scheme 3, regiospecific bromination of **19** provided the corresponding 5-bromo-3-furoic acid **20**.[17] Metal-halogen exchange and silylation of the dianion derived from **20** gave **21**.[18] Reduction and bromination of acid **21** afforded the desired bromomethyl furan **23**.[19] Alkylation of ethyl acetoacetate with **23** provided furyl ester **24** in 85% yield.[12] Finally, peracetic acid oxidation of ester **24** gave butenolide **15**.[20] Again, a similar transformation of butenolide **15** generated the model compound **8** via **16**, **5**, **17** and **18**, as illustrated in Scheme 2

Scheme 3.



In order to test the possibility of executing an intramolecular Michael addition for the tertiary hydroxy group-containing lactone **40**, we synthesized spiroether **9** from the commercially available 3-furancarboxylic acid (**19**) (Scheme 4). All attempts to convert the butenolide **16** (see Scheme 2) to lactone **40** using methyllithium were unsuccessful. This was mainly due to the chemoselectivity problem involving the ketone and the α,β-unsaturated lactone. In light of this fact, we decided to modify our previous strategy for the realization of the model compound **9**. The ultimate synthetic route for **9** is depicted in Scheme 4. The synthesis of furan **29** from acid **19** was straightforward.[12] Addition of methyllithium to **29** gave the desired hydroxyfuran **6**.[21] The deprotonation-silylation of **6**,[22] on the other hand, gave an inseparable mixture of **31** and **33**, whose yields were determined by NMR spectrometry, together with a smaller amount of the isolable **35**. Fortunately, peracid oxidation [20] of a mixture of **31** and **33** afforded a chromatographically separable mixture of **36** and **38**. Desilylation of **36** furnished **40**.[23] An intramolecular Michael addition of **40** was triggered by potassium carbonate, furnishing **42**.[15] The structure of lactone **42** was confirmed by its ^{1}H NMR (Table 1) and ^{13}C NMR (Table 2) spectrometric studies, as well as by its MS and elemental analysis. Finally, the construction of the desired spiroether **9** was accomplished by reduction[16] of **42** to **44**, whose hydroxyl group was removed by silane reduction.[16] Comparison of the ^{1}H NMR (Table 3) and ^{13}C NMR (Table 4) data of **9** with **8** substantiated the structure of **9**.

Scheme 4.



Encouraged by the above results, we thus set forth to extend our strategy for the conversion of lactol **44** to an unsaturated spiroether. In order to generate an unsaturated ether, lactol **44** was treated with 3 equivalents of $MeSO_2Cl$ and 3.5 equivalents of pyridine in dichloromethane at room temperature.[24] Dehydration of lactol **44** directly to the enol ether using this method was however unfruitful. Ley and coworkers also reported an unsuccessful example of this direct dehydration in their synthesis of a model compound related to azadirachtin.[25] The above unsatisfactory outcome probably resulted from the instability of the unsaturated

spiroether in acidic condition. On the other hand, the low boiling point of the unsaturated spiroether might also cause considerable difficulties in its handling. Based on aforementioned consideration, we therefore attempted to replace the methyl groups of lactol **44** with phenyl groups. Again, a similar transformation of 3-furancarboxylic acid (**19**) generated spiroether **10**, via alcohol **25**, bromide **26**, ester **28**, ketone **30**, alcohol **7**, 2-trimethylsilyl substituted furan **32** and **34**, butenolide **37**, hydroxybutenolide **41**, spirolactone **43** and lactol **45**. Subsequent oxidation and elimination[25] of phenylsulfide **46** prepared from **45** eventually yielded **11**. The structure of **11** was confirmed by its ^{1}H NMR (Table 3) and ^{13}C NMR (Table 4) spectral data, as well as by its MS and elemental analysis. ^{1}H NMR spectra of **47** and **11** indicated the conversion of the phenylsulfinyl group of **47** into the double bond of **11** (δ 6.55, J = 2.6 Hz, and δ 5.09, J = 2.6 Hz for H-8 and δ 5.09, J = 2.6 Hz for H-9 of **11** versus δ 4.65-4.72 for H-8 and δ 2.10-2.20 and δ 3.05-3.15, J = 4.1, 7.4 Hz for two H-9 of **47**). On the other hand, the ^{13}C signals for C-8 and C-9 of **11** were shifted downfield to δ 149.1 and δ 106.2, respectively relative to those of the saturated spiroether **10** (δ 77.5 for C-8 and δ 34.9 for C-9).

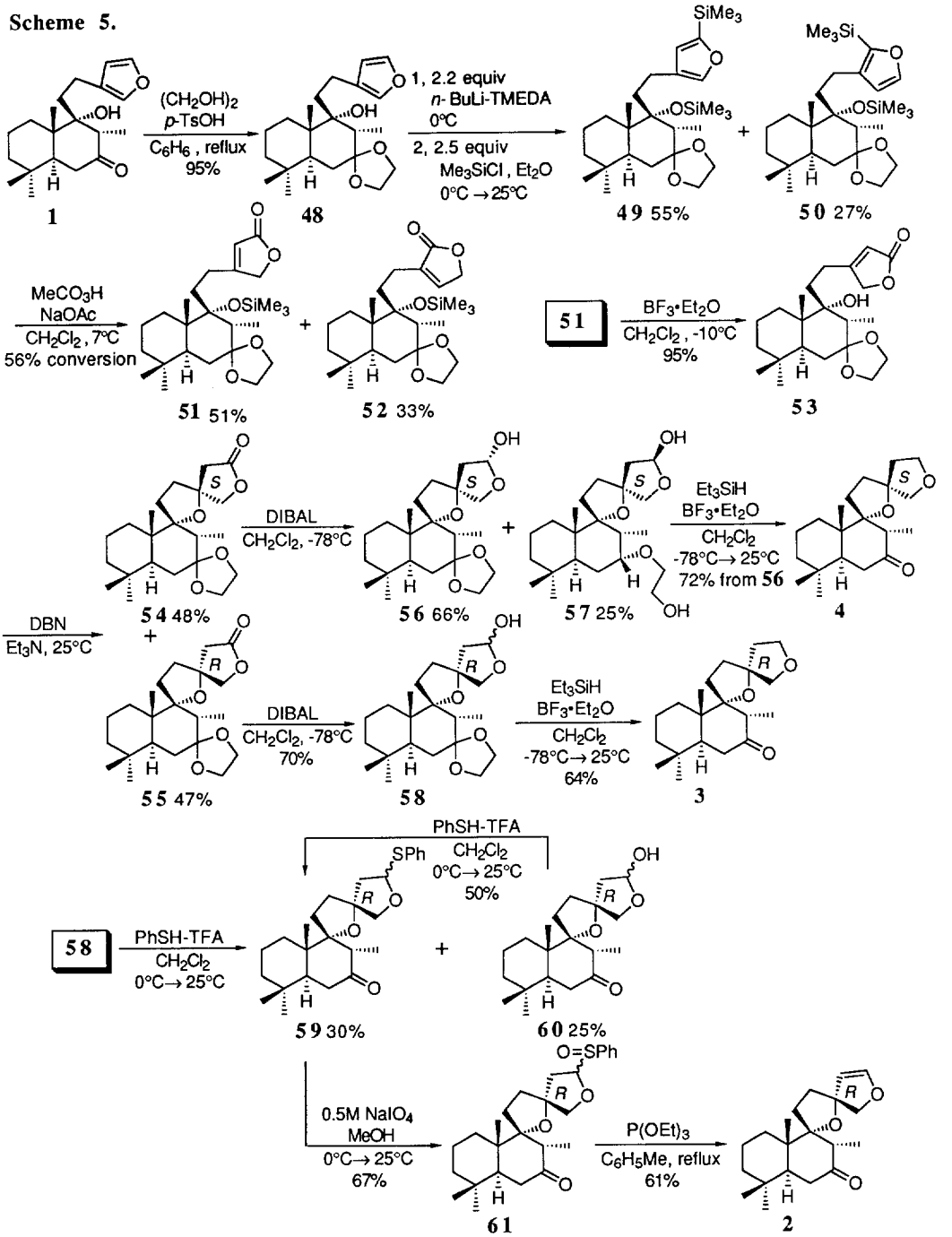
Synthesis of Natural Products

Having secured a reliable approach to realize both spirotetrahydrofuran **8**, **9** as well as **10** and spirodihydrofuran **11**, similar routes were then utilized to construct natural products **2**, **3** and **4** from the readily available **1**.[1d] As shown in Scheme 5, protection of the keto group of **1** gave **48**. As anticipated, deprotonation and silylation of **48** yielded a mixture of **49** and **50**, which was not separated and was oxidized with peracid to furnish a chromatographically separable mixture of butenolides **51** and **52**. Desilylation of **51** converted it to the key intermediate **53**, which underwent an intramolecular Michael addition[26] to give again a chromatographically separable mixture of a pair of diastereomers **54** and **55**, the only stereochemical difference being the 13*S* or 13*R* configuration, respectively. Unlike the intramolecular Michael cyclization of **5**, **40** and **41**, It is noteworthy that a similar reaction of **53** utilizing potassium carbonate[15] led only to an inferior yield of **54** and **55**. On the other hand, treatment of **5** and **40** with DBN-Et_3N[26] did not provide better yields of the lower-boiling **17** and **42** respectively due to the work-up difficulty in removing completely the higher boiling bases. It is significant to note that the biosynthetic pathway leading to the absolute configuration of the spiro carbon (C-13) in **2** is probably also non-enantiospecific, because two related compounds, namely scutellone B and scutellone G have been isolated and identified.[27]

The 13*S* configuration of **54** was established by X-ray crystallographic analysis of **57** which was a side product of the DIBAL reduction of **54**. The X-ray crystallographic analysis of **57**[1a] unequivocally certified its 13*S* configuration. Further conversion (deprotection and silane reduction) of **56** led to the "non-natural" **4**, whose spiro carbon C-13 must be also of *S* configuration.

In principle, the verification of the 13*S* configuration of **54** also indirectly confirmed the 13*R* configuration of **55**, which was likewise reduced to **58**. Compound **3** was obtained upon silane reduction and concomitant deprotection of the ketal group, presumably due to the Lewis acid condition. The physical and spectroscopic properties of **3** were identical with those of a "natural" **3** obtained through catalytic hydrogenation of the natural **2**.[1d] However, it was necessary to apply a modified Ley procedure[25] to convert **58** to **2**, presumbly due to the interference of the C-7 keto group regenerated during the conversion of **58** to **59**. Thermal elimination of **61** eventually gave **2**, whose physical and spectral data were identical to those of the natural **2**.[1d]

Scheme 5.



To conclude, we have devised a general synthetic strategy, by which both **2** and **3**, as well as their respective (13*S*)-diastereomer **4** could be obtained from a common key intermediate **1**. In order to complete the total synthesis of **2**, an enantiospecific synthesis of the likely less synthetically demanding **49** is in

progress. Moreover, the diastereoselective Michael cyclization of **53** to either **54** or **55** is also under active investigation.

Experimental Section

All solvents and reagents used were purified by standard procedures. All evaporation of organic solvents was carried out by a rotary evaporator in conjunction with a water aspirator.

NMR spectra were recorded on a Bruker Cryospec WM 250 spectrometer. ^{1}H NMR (250.13 MHz) chemical shifts are reported relative to $CDCl_3$ at δ 7.24 ppm and Me_4Si at δ 0.00 ppm. Coupling parameters are reported in Hz. ^{13}C NMR (62.89 MHz) chemical shifts are expressed relative to $CDCl_3$ at δ 77.00 ppm and Me_4Si at δ 0.00 ppm. NMR spectral terms are reported according to the following abbreviations: s, singlet; d, doublet; t, triplet; m, multiplet; dd, doublet of doublets. Mass spectra (EIMS and HRMS, VG Micromass 7070F spectrometer) were determined at an ionizing voltage 70 eV, relevant data were tabulated as *m/z*. IR spectra were run on a JASCO A-100 infrared spectrophotometer. Elemental analyses were performed at Shanghai Institute of Organic Chemistry, The Chinese Academy of Sciences, China.

Flash column chromatography was performed using E. Merck silica gel 60 (230-400 mesh). The plates used for thin-layer chromatography (TLC) were E. Merck silica gel $60F_{254}$ (0.25 mm thick) precoated on an aluminum plate.

Melting points were measured on a hot-stage and are uncorrected.

3,3-Bis(bromomethyl)acrylic acid (13)[11]

A solution of **12** (30 g, 0.3 mol) and NBS (118 g, 0.66 mol) in CCl_4 (600 mL) was heated under reflux for 3h during which benzoyl peroxide (0.9 g) was added in small portions at 20 min intervals. After heating for an additional 1h, the reaction mixture was allowed to cool to rt. The precipitated succinimide was removed by filtration, and the filtrate evaporated under reduced pressure to give a crude **13** which was chromatographed on silica gel (elution with hexanes-ethyl acetate, 4:1) to afford 74 g (95%) of **13** as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 4.20 (s, 2H), 4.67 (s, 2H), 6.08 (s, 1H), 10.30 (s, 1H); MS *m/z* 256 (M^+, 0.17), 258 (M^++2, 0.42), 260 (M^++4, 0.13).

3-Bromomethyl-2-buten-4-olide (14)[11]

To the acid **13** (40 g, 0.16 mol) at rt was added dropwise 5% NaOH (130 mL) over 1h, and the milky solution was stirred at rt for 12h. The reaction mixture was extracted with CH_2Cl_2 (3x100 mL), and the combined extracts were washed with saturated $NaHCO_3$ (2x40 mL) and brine (2x100 mL) and dried over anhydrous Na_2SO_4. Concentration and chromatography of the residue on silica gel (elution with hexanes-ethyl acetate, 4:1) afforded 19 g (70%) of **14** as a colorless oil: [lit[11] bp 118-121℃, (0.6 mmHg)]; ^{1}H NMR ($CDCl_3$) δ 4.18 (s, 2H), 5.00 (m, 2H), 6.18 (m, 1H); MS *m/z* 176 (M^+, 5.62), 178 (M^++2, 7.03).

3-(3-Oxo-2-ethoxycarbonylbutyl)-2-buten-4-olide (15)

Method A—Alkylation Method[12]

To a suspension of NaH (7.48 g, 0.24 mol, 20% mineral oil) in THF (150 mL) at 0℃ was added dropwise ethyl acetoacetate (28.6 mL, 0.23 mol). The pale yellow solution was stirred at 0℃ for 30 min. Then the freshly prepared anion solution was added to **14** (20 g, 0.11 mol) at rt. After 6h, the mixture was quenched with 1N HCl (100 mL), and diluted with ether (300 mL). The organic layer was separated and washed with water (2x50 mL) and brine (2x70 mL), and then dried over anhydrous Na_2SO_4. Concentration and

chromatography of the residue on silica gel (elution with hexanes-ethyl acetate, 2:1) afforded 22 g (85%) of **15** as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.17 (t, *J*=7.2 Hz, 3H), 2.19 (s, 3H), 2.81 (d, *J*=7.2 Hz, 2H), 3.75 (t, *J*=7.2 Hz, 3H), 4.66 (brs, 2H), 5.70 (t, *J*=1.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 13.8, 26.1, 28.9, 57.3, 61.9, 73.0, 116.5, 166.7, 167.9, 173.1, 200.2; MS *m/z* 226 (M^+, 6.94); Anal. Calcd. for $C_{11}H_{14}O_5$: C, 58.39; H, 6.24. Found: C, 57.77; H, 6.23.

Method B—Peracetic Acid Method[20]

To a stirred solution of 32% peracetic acid (0.48 mL, 7.08 mmol) and powdered anhydrous NaOAc (0.58 g, 7.08 mmol) in CH_2Cl_2 (5 mL) at 0℃ was added a solution of **24** (0.5 g, 1.77 mmol) in CH_2Cl_2 (1 mL). After the mixture was stirred at 7℃ for 4 h, saturated $NaHCO_3$ (1 mL), and 10% $Na_2S_2O_3$ solution (6 mL) were added. The aqueous layer was extracted with ether (3x50 mL). The combined extracts were washed with brine (2x20 mL), and dried over anhydrous Na_2SO_4. Concentration and chromatography of the residue on silica gel (elution with hexanes-ethyl acetate, 1:1) afforded 0.24 g (60%) of **15** as a colorless oil. The spectroscopic data of **15** are identical with an authentic sample prepared previously.

3-(3-Oxobutyl)-2-buten-4-olide (16)[13]

To a stirred solution of 5% NaOH (60 mL, 75 mmol) at rt was added the ester **15** (6 g, 26.55 mmol). The mixture was stirred at rt for 3 h, then 2N HCl was added until the reaction mixture was acidic (pH 2-3) and the stirring was continued at 50℃ for 1h. The mixture was extracted with ether (3x100 mL). The combined extracts were washed with brine (2x50 mL), and dried over anhydrous Na_2SO_4. Concentration and chromatography of the residue on silica gel (elution with dichloromethane-ethyl acetate, 2:1) afforded 2.9 g (70%) of **16** as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 2.22 (s, 3H), 2.66 (t, *J*=5 Hz, 2.5 Hz, 2H), 2.80 (t, *J*=5 Hz, 2.5 Hz, 2H), 4.76 (t, *J*=2.5 Hz, 2H), 5.80 (t, *J*=2.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 22.1, 29.6, 40.5, 73.1, 115.6, 169.1, 173.5, 205.5; Ms *m/z* 154 (M^+, 18.28); HRMS: *m/z* (M^+) calcd for $C_8H_{10}O_3$ 154.0630; found: 154.0643.

3-(3-Hydroxybutyl)-2-buten-4-olide (5)[14]

To a stirred solution of **16** (1.4 g, 9.09 mmol) in dry THF (20 mL) at 0℃ was added $NaBH_4$ (0.1 g, 2.64 mmol) in portions. The mixture was stirred until TLC analysis showed that the reaction was complete (about 3h). The mixture was diluted with water (5 mL) and acidified with 2N HCl (3 mL) until neutral. The mixture was extracted with ether (3x30 mL), and dried over anhydrous Na_2SO_4. Concentration and chromatography of the residue on silica gel (elution with ethyl acetate) afforded 0.9 g (63%) of **5** as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.22 (d, *J*=7.5 Hz, 3H), 1.72 (q, *J*=7.5 Hz, 2H), 2.49-2.56 (m, 2H), 2.65-2.72 (m, 1H), 3.86 (quint., *J*=7.5 Hz, 1H), 4.78-4.81 (d, *J*=2.5 Hz, 2H), 5.86 (t, *J*=2.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 23.4, 24.7, 36.1, 66.6, 73.1, 115.0, 170.9, 174.2; MS *m/z* 156 (M^+, 2.43), 157 (M^++1, 27.16); Anal. Calcd. for $C_8H_{12}O_3$: C, 61.51; H, 7.75. Found: C, 61.46; H, 7.75.

2-Methyl-1,7-dioxaspiro[4.4]nonan-8-one (17)[15]

A mixture of **5** (0.1 g, 0.64 mmol) and K_2CO_3 (25.57 mg, 0.18 mmol) in MeOH (1.5 mL) was stirred at rt for 15 min and then the mixture was diluted with water (2 mL), and extracted with ether (3x15 mL). The combined extracts were washed with brine (2x10 mL), and dried over anhydrous Na_2SO_4. Concentration and chromatography of the residue on silica gel (elution with dichloromethane-ethyl acetate, 9:1) afforded 30 mg (43%, 30 mg of starting material was recovered) of **17** as a colorless oil, which consisted of a 1:1 mixture of diastereomers of **17**: ^{1}H NMR ($CDCl_3$) (**A** isomer) δ 1.25 (d, *J*=6 Hz, 3H), 1.53-1.62 (m, 1H), 1.94-2.24 (m, 3H), 2.53-2.77 (m, 2H), 4.03-4.32 (m, 3H) (see Table 1 for detailed assignment); (**B** isomer) δ 1.26 (d, *J*=6 Hz, 3H), most of the other signals partially overlap with those of isomer **A**; IR (film) C=O, (1780, 1739 cm^{-1});

^{13}C NMR (C_6D_6) (most carbons show two peaks because of diastereomerism) δ 21.1, 21.2, 32.9, 33.3, 33.7, 34.1, 40.6, 41.3, 75.3, 75.4, 76.9, 77.6, 84.5, 84.6, 174.1, 174.3; MS *m/z* 156 (M^+, 49.79), 157 (M^++1, 6.93); Anal. Calcd. for $C_8H_{12}O_3$: C, 61.51; H, 7.75. Found: C, 61.82; H, 7.70.

2-Methyl-1,7-dioxaspiro[4.4]nonan-8-ol (18)[16]

To a solution of **17** (60 mg, 0.385 mmol) in toluene (1.7 mL) cooled at -78℃ was slowly added DIBAL in hexane (1M, 0.77 mL, 0.77 mmol). After 40 min, the mixture was poured into a rapidly stirred mixture of ice (1 g) and HOAc (0.2 mL), and then $CHCl_3$ (20 mL) was added. The two-phase system was stirred vigorously at rt for 60 min. The organic layer was separated and washed with saturated $NaHCO_3$ (7 mL), and brine (2x7 mL). Concentration and chromatography of the residue on silica gel (elution with dichloromethane-ethyl acetate, 9:1) afforded 40 mg (66%) of **18** as a colorless oil, which consisted of a 1:1 mixture of diastereomers of **18**: ^1H NMR ($CDCl_3$) (**A** isomer) δ 1.25-1.35 (m, 3H), 1.53-1.62 (m, 1H), 1.94-2.22 (m, 4H), 3.70-3.85 (m, 2H), 4.15-4.20 (m, 2H) 5.45 (br s, 1H); (**B** isomer), most of the other signals partially overlap with those of isomer **A**; ^{13}C NMR ($CDCl_3$) (most carbons show two peaks because of diastereomerism) δ 21.2, 21.3, 32.1, 32.6, 33.4, 44.6, 45.6, 75.5, 75.8, 77.5, 77.8, 88.5, 98.9, 99.5; MS *m/z* 158 (M^+, 0.58), 159 (M^++1, 0.67); Anal. Calcd. for $C_8H_{14}O_3$: C, 60.72; H, 8.92. Found: C, 60.95; H, 9.20.

2-Methyl-1,7-dioxaspiro[4.4]nonane (8)[16]

To a solution of **18** (50 mg, 0.32 mmol) and Et_3SiH (76 μL, 0.48 mmol) in CH_2Cl_2 (2 mL) at -78℃ was slowly added BF_3•Et_2O (47 μL, 0.38 mmol). After 3h, a saturated $NaHCO_3$ solution (0.5 mL) was introduced, and the cooling bath was removed and the solution allowed to warm to rt with vigorous stirring. The mixture was diluted with ether (50 mL), the organic layer was separated, and washed with 10% $NaHCO_3$ (2x5 mL) and brine (10 mL). Concentration under reduced pressure and chromatography of the residue on silica gel (elution with dichloromethane-ethyl acetate, 5:1) afforded 21 mg (46%) of **8** as a low-boiling colorless liquid, which consisted of a 1:1 mixture of diastereomers of **8**: ^1H NMR (C_6D_6) (**A** isomer) δ 1.27 (d, *J*=6 Hz, 3H), 1.51-1.60 (m, 1H), 1.82-2.10 (m, 5H), 3.60-3.80 (m, 2H), 3.83-4.12 (m, 3H); (**B** isomer) δ 1.28 (d, *J*=6 Hz, 3H), most of the other signals partially overlap with those of isomer **A**; HRMS: *m/z* (M^+-1) calcd for $C_8H_{14}O_2$ 141.0912; found: 141.0720.

5-Bromo-3-furoic acid (20)[17]

To a solution of pyridinium hydrobromide perbromide (57 g, 0.18 mol) in HOAc (70 mL) was added 3-furoic acid (**19**) (20 g, 0.17 mol). The reaction mixture was heated to 35-40℃ for 5 h. The hydrogen bromide formed was swept by a steam of N_2. Then the solvent was evaporated under reduced pressure, and the remaining solid was suspended in water, filtered, dried, and sublimed under reduced pressure (106-108℃, 5 mm Hg) to give 20.5 g (60%) of **20** as a white solid: mp 136-137℃, (lit[17] mp 138-139℃); ^1H NMR ($CDCl_3$) δ 6.71 (d, *J*=1.2 Hz,1H), 8.03 (d, *J*=1.2 Hz, 1H), 9.87 (br s, 1H); ^{13}C NMR (DMSO-d_6) δ 111.1, 122.3, 123.1, 149.2, 162.5.

5-Trimethylsilyl-3-furoic acid (21)[18]

To a stirred solution of **20** (8 g, 41.89 mmol) in dry ether (80 mL) under N_2 at -78℃ was added dropwise *n*-butyllithium in hexane (1.6 M, 57.6 mL, 92.16 mmol). The mixture was stirred at -78℃ for 40 min and then trimethylsilylchloride (TMSCl) (13.2 mL, 104.8 mmol) was added dropwise with stirring at -78℃. The mixture was stirred at -78℃ for 10 min and then the mixture was allowed to reach rt. The stirring was continued for 2 h at rt, then diluted with water (50 mL) and acidified with 2N HCl (150 mL). The mixture was vigorously stirred for 30 min, then diluted with water (150 mL) and extracted with ether (3x100 mL). The

combined extracts were washed with brine (3x50 mL), dried over anhydrous Na_2SO_4 and evaporated to leave a residure which was chromatographed on silica gel (elution with hexanes-ethyl acetate, 1:1) to give 4.7 g (61%) of **21**[18] as a white solid: mp 85-86°C; ^1H NMR ($CDCl_3$) δ 0.29 (s, 9H), 6.96 (s, 1H), 8.28 (s, 1H) ca 10 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ -1.96(3), 118.8, 119.3, 153.0, 163.0, 169.2; MS *m/z* 184 (M^+, 18.07), 185 (M^++1, 2.15).

5-Trimethylsilyl-3-furylmethanol (22)[28]

To a stirred solution of $LiAlH_4$ (1.28 g, 33.7 mmol) in dry ether (20 mL) was added at a rate such as to produce a gentle reflux, a solution of **21** (5 g, 27.13 mmol) in dry ether (30 mL). After 2h, water (30 mL) was added cautiously to decompose the excess hydride at 0°C. Then 10% H_2SO_4 (45 mL) was added (the flask was cooled in an ice-water bath). The reaction mixture was extracted with ether (3x50 mL). The combined extracts were washed with brine (2x20 mL), and dried over anhydrous Na_2SO_4. Concentration and chromatography of the residue on silica gel (elution with hexanes-ethyl acetate, 4:1) afforded 4.2 g (90%) of **22** as a colorless oil: ^1H NMR ($CDCl_3$) δ 0.36 (s, 9H), 4.24 (s, 2H), 6.63 (s, 1H), 7.56 (s, 1H); ^{13}C NMR ($CDCl_3$) δ -1.62 (3), 55.72, 119.6, 124.9, 143.9, 161.0; MS *m/z* 170 (M^+, 45.20), 171 (M^++1, 5.68).

2-Trimethylsilyl-4-bromomethylfuran (23)[19]

To a stirred solution of **22** (2 g, 0.012 mol) and CBr_4 (4.88 g, 0.02 mol) in CH_2Cl_2 (30 mL) at 0°C was added portionwise triphenyl phosphine (4.8 g, 0.02 mol). After the addition was completed, the mixture was stirred for an additional 1h, and then the solvent was removed in vacuo. Ether (30 mL) was added and the mixture filtered. The filter cake was washed with ether (3x50 mL). The combined filtrate and washings were concentrated in vacuo to give a residure which was chromatographed on silica gel (elution with hexanes-ethyl acetate, 6:1) to afford 2.4 g (86%) of **23** as a colorless oil: ^1H NMR ($CDCl_3$) δ 0.65 (s, 9 H), 4.67 (s, 2H), 6.94 (s, 1H), 7.94 (s, 1H). Compound **23** was used immediately in the next step without further purification and characterization.

4-(3-Oxo-2-ethoxycarbonylbutyl)-2-trimethylsilylfuran (24)[12]

To a suspension of NaH (0.56 g, 18.85 mmol, 20% mineral oil) in THF (20 mL) at 0°C was added dropwise ethyl acetoacetate (2.17 mL, 17.14 mmol). The pale yellow solution was stirred at 0°C for 30 min. Then the freshly prepared anion solution was added to **23** (2 g, 8.57 mmol) at rt. After 6h, the mixture was quenched with 1N HCl (10 mL), and diluted with ether (100 mL). The organic layer was separated and washed with water (40 mL) and brine (2x40 mL), and then dried over anhydrous Na_2SO_4. Concentration and chromatography of the residue on silica gel (elution with hexanes-ethyl acetate, 5:1) afforded 2 g (85%) of **24** as a colorless oil: ^1H NMR ($CDCl_3$) δ 0.21 (s, 9H), 1.25 (t, *J*=7.0 Hz, 3H), 2.21 (s, 3H), 2.98 (d, *J*= 7.5 Hz, 2H), 3.15 (t, *J*=7.5 Hz, 1H), 4.17 (q, *J*=7.1 Hz, 2H), 6.49 (s, 1H), 7.45 (s, 1H); ^{13}C NMR ($CDCl_3$) δ -1.72 (3), 13.9, 25.3, 29.2, 60.6, 61.4, 103.8, 120.8, 121.2, 143.9, 169.2, 202.1; MS *m/z* 282 (M^+, 20.66); Anal. Calcd. for $C_{14}H_{22}O_4Si$: C, 59.52; H, 7.86. Found: C, 59.45; H, 7.46.

3-Furylmethanol (25)[28]

To a stirred solution of $LiAlH_4$ (4.2 g, 111 mmol) in dry ether (40 mL) was added at a rate such as to produce a gentle reflux, a solution of **19** (10 g, 89.2 mmol) in dry ether (60 mL). After 2h, water (120 mL) was added cautiously to decompose the excess hydride at 0°C. Then 10% H_2SO_4 (150 mL) was added (the flask was cooled in an ice-water bath). The reaction mixture was extracted with ether (3x100 mL). The combined extracts were washed with brine (3x60 mL), and dried over anhydrous Na_2SO_4. Concentration and chromatography of the residue on silica gel (elution with hexanes-ethyl acetate, 3:1) afforded 8 g (91%) of **25** as a colorless oil:

[lit[28] bp 54-55°C, (2 mmHg)]; ^{1}H NMR ($CDCl_3$) δ 3.28 (brs, 1H), 4.44 (s, 2H), 6.38 (t, *J*=1.6 Hz, 1H), 7.36 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 55.2, 109.4, 124.8, 139.2, 142.6.

3-Bromomethylfuran (26)[19]

To a stirred solution of **25** (8 g, 0.08 mol) and CBr_4 (32 g, 0.096 mol) in CH_2Cl_2 (100 mL) at 0°C was added portionwise triphenyl phosphine (33 g, 0.126 mol). After the addition was completed, the mixture was stirred for an additional 2h, and then the solvent was removed in vacuo. Ether (100 mL) was added and the mixture filtered. The filter cake was washed with ether (3x100 mL). The combined filtrate and washings were concentrated in vacuo to give a residue which was chromatographed on silica gel (elution with hexanes-ethyl acetate, 5:1) to afford 12.5 g (95%) of **26** as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 4.36 (s, 2H), 6.44 (s, 1H), 7.39 (s, 1H), 7.47 (s, 1H). Compound **26** was used immediately in the next step without further purification and characterization.

Ethyl 2-(3-furylmethyl)acetoacetate (27) and **Ethyl 2-(3-furylmethyl)benzoylacetate (28)**[12]

To a suspension of NaH (1.64 g, 54.65 mmol, 20% mineral oil) in THF (20 mL) at 0°C was added dropwise ethyl acetoacetate (6.3 mL, 49.68 mmol). The pale yellow solution was stirred at 0°C for 30 min. Then the freshly prepared anion solution was added to **26** (4 g, 24.84 mmol) at rt. After 6h, the mixture was quenched with 1N HCl (40 mL), and diluted with ether (90 mL). The organic layer was separated and washed with water (2x30 mL) and brine (2x40 mL) and then dried over anhydrous Na_2SO_4. Concentration and chromatography of the residue on silica gel (elution with hexanes-ethyl acetate, 5:1) afforded 4.6 g (88%) of **27** as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.24 (t, *J*=7.0 Hz, 3H), 2.23 (s, 3H), 2.98 (d, *J*= 7.5 Hz, 2H), 3.69 (t, *J*=7.5 Hz, 1H), 4.18 (q, *J*=7.1 Hz, 2H), 6.24 (s, 1H), 7.24 (s, 1H), 7.34 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.7, 24.1, 29.9, 61.1, 62.1, 111.6, 121.9, 140.6, 143.9, 169.7, 202.7; MS *m/z* 210 (M^+, 16.22); Anal. Calcd. for $C_{11}H_{14}O_4$: C, 62.83; H, 6.72. Found: C, 62.65; H, 6.81.

The similar procedure was repeated using NaH (8.19 g, 0.27 mol, 20% mineral oil) in THF (110 mL), ethyl benzoylacetate (43 mL, 0.25 mol) and **26** (20 g, 0.12 mol) to afford, after chromatography on silica gel (elution with hexanes-ethyl acetate, 10:1), 30.4 g (90%) of **28** as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.11 (t, *J*=7 Hz, 3H), 3.15 (d, *J*=7.3 Hz, 2H), 4.10 (q, *J*=7 Hz, 2H), 4.57 (t, *J*=7.3 Hz, 1H), 6.27 (t, *J*=0.8 Hz, 1H), 7.24 (d, *J*= 0.8 Hz, 1H), 7.28 (d, *J*=1.4 Hz, 1H), 7.43 (t, *J*=7.4 Hz, 2H), 7.55 (dd, *J*=1.5, 7.4 Hz, 1H), 7.98 (dd, *J*=1.5 Hz, 7.4 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 13.6, 23.9, 54.8, 61.2, 110.8, 121.2, 128.4(2), 133.3, 135.9, 139.7, 142.7, 168.9, 194.2; MS *m/z* 272 (M^+, 7.72); Anal. Calcd. for $C_{16}H_{16}O_4$: C, 70.56; H, 5.93. Found: C, 70.31; H, 5.97.

3-(3-Oxobutyl)furan (29) and **3-(3-Oxo-3-phenylpropyl)furan (30)**[13]

To a stirred solution of 5% NaOH (30 mL, 37 mmol) at rt was added the ester **27** (4.59 g, 0.022 mol). The mixture was stirred at rt for 3 h, then 2N HCl was added until the reaction mixture was acidic (pH 2-3) and the stirring was continued at 50°C for 1h. The mixture was extracted with ether (3x60 mL). The combined extracts were washed with brine (2x40 mL), and dried over anhydrous Na_2SO_4. Concentration and chromatography of the residue on silica gel (elution with hexanes-ethyl acetate, 5:1) afforded 2.41 g (80%) of **29** as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 2.15 (s, 3H), 2.69 (s, 4H), 6.25 (s, 1H), 7.22 (s,1H), 7.34 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 18.8, 29.5, 43.5, 110.9, 124.0, 138.9, 142.8, 207.6; MS *m/z* 138 (M^+, 4.86); Anal. Calcd. for $C_8H_{10}O_2$: C, 69.54; H, 7.29. Found: C, 69.57; H, 6.91.

The similar procedure was repeated using 5% NaOH (100 mL, 125 mmol) and ester **28** (15 g, 55 mmol) to afford, after chromatography on silica gel (elution with hexanes-ethyl acetate, 10:1), 7.8 g (71%) of **30** as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 2.87 (t, *J*=7.3 Hz, 2H) 3.22 (t, *J*=7.3 Hz, 2H), 7.14 (s, 1H), 7.27 (d, *J*=1.4

Hz,1H), 7.34 (d, *J*=1.4 Hz, 1H), 7.45 (t, *J*=7 Hz, 2H), 7.54 (dd, *J*=1.4, 7.4 Hz, 1H), 7.96 (dd, *J*=1.4, 7.4 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 19.3, 39.0, 110.9, 124.1, 127.9, 128.5, 132.9, 137.0, 139.1, 142.8, 199.0; MS *m/z* 200 (M^+, 10.24); Anal. Calcd. for $C_{13}H_{12}O_2$: C, 77.97; H, 6.04. Found: C, 77.66; H, 5.94.

3-(3-Hydroxy-3-methylbutyl)furan (6) and 3-(3-Hydroxy-3,3-diphenylpropyl)furan (7)[21]

To a stirred solution of **29** (7 g, 50.64 mmol) in dry ether (50 mL) under N_2 at -78℃ was added dropwise MeLi in ether (1.4M, 54.25 mL, 75.96 mmol). The mixture was stirred at -78℃ for 30 min before the mixture was allowed to reach rt and the stirring was continued for an additional 5h. The mixture was diluted with water (50 mL) and acidified with 2N HCl (30 mL), and extracted with ether (3x100 mL). Concentration and chromatography of the residue on silica gel (elution with hexanes-ethyl acetate, 5:1) afforded 5.1 g (65%) of **6** as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.27 (s, 6H), 1.75 (t, *J*=5.1 Hz, 2H), 2.52 (t, *J*=5.1 Hz, 2H), 6.28 (s, 1H), 7.23 (s, 1H), 7.36 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 20.4, 29.9 (2), 44.7, 71.4, 111.6, 125.8, 139.6, 143.4; MS *m/z* 154 (M^+, 7.81); Anal. Calcd. for $C_9H_{14}O_2$: C, 70.08; H, 9.15. Found: C, 70.30; H, 9.27.

The similar procedure was repeated using **30** (6.4 g, 0.03 mol) in dry ether (30 mL) and phenyllithium in ether (96%, 44.5 mL, 0.07 mol) to afford, after chromatography on silica gel (elution with hexanes-ethyl acetate, 5:1), 8 g (89%) of **7** as a white solid: mp 78-79℃; ^{1}H NMR ($CDCl_3$) δ 2.34-2.49 (m, 4H), 6.17 (d, *J*=0.6 Hz, 1H), 7.09 (s, 1H), 7.17-7.27 (m, 7H), 7.37 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 19.3, 42.1, 78.0, 110.8, 124.8, 125.8, 125.9, 126.8, 128.1, 138.6, 142.6, 146.7; MS *m/z* 278 (M^+, 2.77); Anal. Calcd. for $C_{19}H_{18}O_2$: C, 81.98; H, 6.52. Found: C, 81.85; H, 6.42.

2-Trimethylsilyl-4-(3-trimethylsiloxy-3-methylbutyl)furan (31), 2-Trimethylsilyl-3-(3-trimethylsiloxy-3-methylbutyl)furan (33), 2,5-Bis(trimethylsilyl)-3-(3-trimethylsiloxy-3-methylbutyl)furan (35), 2-Trimethylsilyl-4-(3-trimethylsiloxy-3,3-diphenylpropyl)furan (32) and 2-Trimethylsilyl-3-(3-trimethylsiloxy-3,3-diphenylpropyl)furan (34)[22]

To a mixture of TMEDA (2.67 mL, 17.84 mmol) and *n*-BuLi in hexane (12.74 mL, 1.4M, 17.84 mmol) at 0℃ was added a solution of **6** (1.25 g, 8.11 mmol) in dry ether (17 mL). After 30 min, TMSCl (2.56 mL, 20.17 mmol) was added at 0℃. After an additional 30 min, the mixture was allowed to reach rt. The stirring was continued at rt for 5h, then the mixture was diluted with water (20 mL), acidified with 2N HCl (20 mL), and extracted with ether (3x100 mL). Concentration and chromatography of the residue on silica gel (elution with hexanes) afforded 1.6 g (64.5%) of a 2:1 mixture of **31** and **33** as well as 0.5 g (16%) of **35**.

Higher R_f isomer **35**: A colorless oil: ^{1}H NMR ($CDCl_3$) δ 0.11 (s, 9H), 0.22 (s, 9H), 0.28 (s, 9H), 1.26 (s, 6H), 1.62 (t, *J*=4.4 Hz, 2H), 2.53 (t, *J*=4.4 Hz, 2H), 6.48 (s, 1H); ^{13}C NMR ($CDCl_3$) δ -0.81(3), -0.32(3), 3.6(3), 21.1, 30.5(2), 47.6, 74.4, 121.9, 136.4, 159.4, 164.6; MS *m/z* 370 (M^+, 1.91); Anal. Calcd. for $C_{18}H_{38}O_2Si_3$: C, 58.37; H, 10.34. Found: C, 58.50; H, 10.30.

Lower R_f isomers **31** and **33** were an inseparable mixture.

Data for **31**: As a colorless oil: ^{1}H NMR ($CDCl_3$) δ 0.16 (s, 9H), 0.26 (s, 9H), 1.27 (s, 6H), 1.71 (t, *J*=3.3 Hz, 2H), 2.48 (t, *J*=3.3 Hz, 2H), 6.52 (s, 1H), 7.41 (s,1H); ^{13}C NMR ($CDCl_3$) δ -1.58(3), 2.61(3), 19.6, 29.9(3), 45.5, 73.7, 111.2, 125.6, 142.8, 145.4; MS *m/z* 298 (M^+, 0.15).

Data for **33**: As a colorless oil: ^{1}H NMR ($CDCl_3$) δ 0.16 (s, 9H), 0.32 (s, 9H), 1.27 (s, 6H), 1.64 (t, *J*=3.3 Hz, 2H), 2.56 (t, *J*=3.3 Hz, 2H), 6.27 (s, 1H), 7.52 (s, 1H); ^{13}C NMR ($CDCl_3$) δ -0.96(3), 2.61(3), 20.6, 29.9(3), 46.8, 73.7, 125.6, 136.0, 153.9, 160.4.

Anal. Calcd. for $C_{15}H_{30}O_2Si_2$: C, 60.37; H, 10.14. Found: C, 60.25; H, 10.21.

The similar procedure was repeated using TMEDA (7.8 mL, 0.052 mol), *n*-BuLi in hexane (37.25 mL, 1.4M, 0.052 mol), **7** (6.6 g, 0.024 mol) in dry ether (50 mL) and TMSCl (7.5 mL, 0.059 mol) to afford, after

chromatography on silica gel (elution with hexanes), 9.8 g of an inseparable mixture of **32** (50%) and **34** (47%).

Data for **32**: As a colorless oil: ^{1}H NMR ($CDCl_3$) δ 0.24 (s, 9H), 0.37 (s, 9H), 2.56-2.63 (m, 2H), 2.78-2.84 (m, 2H), 6.74 (s, 1H), 7.50-7.65 (m, 10H), 7.63 (s, 1H); ^{13}C NMR ($CDCl_3$) δ -1.22(3), 1.90(3), 20.1, 43.0, 80.8, 110.9, 121.0, 126.7, 126.8, 126.9, 127.1, 127.7, 146.0, 147.5, 147.6; MS *m/z* 423 (M^+, 2.11), 422 (M^+-1, 4.17).

Data for **34**: As a colorless oil: ^{1}H NMR ($CDCl_3$) δ 0.21 (s, 9H), 0.54 (s, 9H), 2.45-2.56 (m, 2H), 2.82-2.90 (m, 2H), 6.57 (s, 1H), 7.50-7.65 (m, 10H), 7.82 (s, 1H); ^{13}C NMR ($CDCl_3$) δ -1.63(3), 1.83(3), 19.1, 41.7, 80.7, 126.7, 126.8, 126.9, 127.1, 127.7, 135.4, 142.8, 147.5, 154.5, 160.5.

Anal. Calcd. for $C_{25}H_{34}O_2Si_2$: C, 70.89; H, 8.33. Found: C, 70.86; H, 8.27.

3-(3-Trimethylsiloxy-3-methylbutyl)-2-buten-4-olide (36), 2-(3-Trimethylsiloxy-3-methylbutyl)-2-buten-4-olide (38), 3-(3-Trimethylsiloxy-3,3-diphenylpropyl)-2-buten-4-olide (37) and 2-(3-Trimethylsiloxy-3,3-diphenylpropyl)-2-buten-4-olide (39)[20]

To a stirred solution of 32% peracetic acid (2.29 mL, 34.06 mmol) and powdered anhydrous NaOAc (1.39 g, 17.03 mmol) in CH_2Cl_2 (12 mL) at 0℃ was added a mixture of **31** and **33** (1.27 g, 4.26 mmol) in CH_2Cl_2 (4 mL). After the mixture was stirred at 7℃ for 4 h, saturated $NaHCO_3$ (3 mL), and 10% $Na_2S_2O_3$ solution (15 mL) were added. The aqueous layer was extracted with ether (3x80 mL). The combined extracts were washed with brine (2x40 mL), and dried over anhydrous Na_2SO_4. Concentration and chromatography of the residue on silica gel (elution with hexanes-dichloromethane, 1:1) afforded 330 mg (32%) of **36** and 227 mg (22%) of **38**.

Higher R_f isomer **38** as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 0.08 (s, 9H), 1.23 (s, 6H), 1.65 (t, *J*=6.7 Hz, 2H), 2.33 (t, *J*=6.7 Hz, 2H), 4.74 (s, 2H), 7.06 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 2.46(3), 20.5, 29.7(2), 42.3, 69.9, 73.3, 135.0, 143.4, 174.2; MS *m/z* 153 (M^+-Me_3SiO, 5.41); Anal. Calcd. for $C_{12}H_{22}O_3Si$: C, 59.46; H, 9.15. Found: C, 60.02; H, 10.00.

Lower R_f isomer **36** as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 0.07 (s, 9H), 1.19 (s, 6H), 1.66 (t, *J*=7.0 Hz, 2H), 2.46 (t, *J*=7.0 Hz, 2H), 4.73 (s, 2H), 5.78 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 2.32(3), 23.6, 29.6(2), 41.9, 72.9(2), 114.9, 171.1, 173.9; MS *m/z* 243 (M^++1, 0.35); Anal. Calcd. for $C_{12}H_{22}O_3Si$: C, 59.46; H, 9.15. Found: C, 59.52; H, 9.72.

The similar procedure was repeated using solution of 32% peracetic acid (2.27 mL, 33.73 mmol) and powdered anhydrous NaOAc (2.78 g, 33.89 mmol) in CH_2Cl_2 (6 mL) as well as a solution of a mixture of **32** and **34** (3.6 g, 8.49 mmol) in CH_2Cl_2 (4 mL) to afford, after chromatography on silica gel (elution with hexanes-ethyl acetate, 3:1), 1.05 g (48%, 1.07 g of starting material was recovered) of **37** and 0.74 g (34%) of **39**, respectively.

Higher R_f isomer **37** as colorless needles: mp 93-94℃; ^{1}H NMR ($CDCl_3$) δ 0.24 (s, 9H), 2.56 (t, *J*=7.4 Hz, 2H), 2.93 (t, *J*=7.4 Hz, 2H), 4.97 (s, 2H), 6.16 (s, 1H), 7.57-7.67 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 1.69(3), 23.3, 38.6, 72.9, 80.2, 115.1, 126.8, 127.1, 127.8, 127.9, 146.5, 170.5; MS *m/z* 277 (M^+-Me_3SiO, 0.39); Anal. Calcd. for $C_{22}H_{26}O_3Si$: C, 72.10; H, 7.15. Found: C, 72.01; H, 7.15.

Lower R_f isomer **39** as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 0.24 (s, 9H), 2.49 (t, *J*=6.5 Hz, 2H), 2.91 (t, *J*=6.5 Hz, 2H), 4.92 (s, 2H), 7.24 (s, 1H), 7.46-7.67 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 1.63(3), 20.2, 38.4, 69.8, 80.2, 126.8, 127.7, 134.1, 143.8, 147.0, 173.8; MS *m/z* 277 (M^+-Me_3SiO, 0.59); Anal. Calcd. for $C_{22}H_{26}O_3Si$: C, 72.10; H, 7.15. Found: C, 72.47; H, 6.89.

3-(3-Hydroxy-3-methylbutyl)-2-buten-4-olide (40) and 3-(3-Hydroxy-3,3-diphenylpropyl)-2-buten-4-olide (41)[23]

To a stirred solution of **36** (245 mg, 1.01 mmol) in MeOH (7 mL) at rt was slowly added a solution of 2N HCl (2.5 mL). After 15min, the mixture was diluted with ether (30 mL) and then 2M $NaHCO_3$ (5 mL) was added. The organic layer was separated, the aqueous phase was extracted with ether (2x20 mL). The combined extracts were washed with brine (2x30 mL), and dried over anhydrous Na_2SO_4. Concentration and chromatography of the residue on silica gel (elution with dichloromethane-ethyl acetate, 2:1) afforded 155 mg (90%) of **40** as a colorless oil: ^1H NMR ($CDCl_3$) δ 1.23 (s, 6H), 1.71 (t, *J*=7.1 Hz, 2H), 1.73 (br s, 1H), 2.49 (t, *J*=7.1 Hz, 2H), 4.72 (s, 2H), 5.79 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 23.5, 29.3(2), 40.6, 70.0, 73.1, 115.2, 170.6, 174.0; MS *m/z* 170 (M^+, 7.72); Anal. Calcd. for $C_9H_{14}O_3$: C, 63.49; H, 8.29. Found: C, 62.81; H, 8.92.

The similar procedure was repeated using a solution of **37** (0.96 g, 2.62 mmol) in MeOH (30 mL) and a solution of 2N HCl (5 mL). After 20 min, the solid product was filtered, and recrystallized (from hexanes-ethyl acetate, 1:1) to afford 705 mg (100%) of **41** as colorless needles: mp 127-128℃; ^1H NMR ($CDCl_3$) δ 1.60 (brs, 1H), 2.38 (t, *J*=7.1 Hz, 2H), 2.57 (t, *J*=7.1 Hz, 2H), 4.66 (s, 2H), 5.79 (s, 1H), 7.26-7.42 (m, 10H); ^{13}C NMR (DMF-d_6) δ 22.9, 38.4, 72.8, 76.3, 113.7, 125.7, 125.9, 127.5, 147.7, 172.3, 173.5; MS *m/z* 294 (M^+, 9.92); Anal. Calcd. for $C_{19}H_{18}O_3$: C, 77.53; H, 6.16. Found: C, 77.56; H, 6.05.

2,2-Dimethyl-1,7-dioxaspiro[4.4]nonan-8-one (42) and 2,2-Diphenyl-1,7-dioxaspiro[4.4]nonan-8-one (43)[15]

A mixture of **40** (190 mg, 1.12 mmol) and K_2CO_3 (38.6 mg, 0.28 mmol) in MeOH (4 mL) was stirred at rt for 15 min and then the mixture was diluted with water (5 mL), and extracted with ether (3x30 mL). The combined extracts were washed with brine (2x20 mL), and dried over anhydrous Na_2SO_4. Concentration and chromatography of the residue on silica gel (elution with dichloromethane-ethyl acetate, 9:1) afforded 78 mg (53%, 42 mg of starting material was recovered) of **42** as a colorless oil: ^1H NMR ($CDCl_3$) δ 1.24 (2s, 6H), 1.83 (t, *J*=6.7 Hz, 2H), 2.08 (t, *J*=6.7 Hz, 2H), 2.49-2.69 (ABq, *J*=17.4 Hz, 2H), 4.13-4.23 (ABq, *J*=9.5 Hz, 2H); ^{13}C NMR (C_6D_6) δ 28.8(2), 34.8, 38.8, 41.7, 78.1, 82.0, 84.8, 174.3; MS *m/z* 170 (M^+, 14.26); Anal. Calcd. for $C_9H_{14}O_3$: C, 63.49; H, 8.29. Found: C, 63.74; H, 7.92.

The similar procedure was repeated using a mixture of **41** (700 mg, 2.38 mmol) and K_2CO_3 (173 mg, 1.25 mmol) in MeOH (40 mL) to afford, after chromatography on silica gel (elution with hexanes-ethyl acetate, 3:1), 516 mg (80%, 60 mg of starting material was recovered) of **43** as colorless needles: mp 126-127℃; ^1H NMR ($CDCl_3$) δ 2.11 (t, *J*=5.5 Hz, 2H), 2.70 (t, *J*=5.5 Hz, 2H), 2.54-2.88 (ABq, *J*=17.4 Hz, 2H), 4.14-4.39 (ABq, *J*=9.6 Hz, 2H), 7.21-7.43 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 35.0, 38.4, 41.3, 77.8, 85.4, 89.4, 125.4, 125.5, 127.1, 128.3, 145.9, 146.0,174.8; MS *m/z* 294 (M^+, 48.02); Anal. Calcd. for $C_{19}H_{18}O_3$: C, 77.53; H, 6.16. Found: C, 77.32; H, 5.99.

2,2-Dimethyl-1,7-dioxaspiro[4.4]nonan-8-ol (44) and 2,2-Diphenyl-1,7-dioxaspiro[4.4]nonan-8-ol (45)[16]

To a solution of **42** (74 mg, 0.44 mmol) in CH_2Cl_2 (2 mL) cooled at -78℃ was slowly added DIBAL in hexane (1M, 0.87 mL, 0.87 mmol). After 40 min, the mixture was quenched with MeOH (0.5 mL), and then saturated aqueous Na/K tartrate (2 mL) was added, and the solution was stirred at 0℃ for 1h. The mixture was diluted with CH_2Cl_2 (50 mL), the organic layer was separated and washed with saturated $NaHCO_3$ (7 mL), and brine (2x7 mL). Concentration and chromatography of the residue on silica gel (elution with dichloromethane-

ethyl acetate, 9:1) afforded 50 mg (67%) of **44** as a colorless oil, which consisted of a 1:1 mixture of diastereomers of **44**: ^{1}H NMR ($CDCl_3$) (**A** isomer) δ 1.24 (2s, 6H), 1.79-1.94 (m, 2H), 1.98-2.35 (m, 2H), 3.67-3.92 (ABq, *J*=9.0 Hz, 2H), 4.08-4.29 (ABq, *J*=11.8 Hz, 2H), 5.38 (m, 1H); (**B** isomer) δ 1.26 (2s, 6H), most of the other signals partially overlap with those of isomer **A**; ^{13}C NMR (C_6D_6) (most carbons show two peaks because of diastereomerism) δ 28.9, 29.2, 33.5, 35.4, 38.8, 39.0, 46.4, 48.0, 77.4, 77.6, 80.7, 81.9, 88.8, 89.1, 99.3, 99.7; MS *m/z* 172 (M^+, 1.06); Anal. Calcd. for $C_9H_{16}O_3$: C, 62.75; H, 9.37. Found: C, 62.08; H, 7.94.

The similar procedure was repeated using a solution of **43** (182 mg, 0.62 mmol) in CH_2Cl_2 (7 mL) and DIBAL in hexane (1.24 mL, 1M, 1.24 mmol) to afford, after chromatography on silica gel (elution with hexanes-ethyl acetate, 2:1), 148 mg (81%) of **45** as a colorless oil, which consisted of a 1:1 mixture of diastereomers of **45**: ^{1}H NMR ($CDCl_3$) (**A** isomer) δ 1.91-2.15 (m, 3H), 2.49-2.71 (m, 3H), 4.39 (d, *J*=9.1 Hz, 1H), 3.65-4.25 (ABq, *J*=9.2 Hz, 2H), 5.48 (m, 1H), 7.21-7.39 (m, 10H); (**B** isomer), most of other signals partially overlap with those of isomer **A**; ^{13}C NMR ($CDCl_3$) (most carbons show two peaks because of diastereomerism) δ 32.9, 35.2, 38.7, 39.1, 45.5, 47.0, 77.5, 88.3, 89.6, 98.9, 99.5, 125.6, 125.7, 125.9, 126.0, 126.6, 126.9, 127.3, 128.0, 128.2, 128.3, 146.1, 146.3; MS *m/z* 296 (M^+, 2.22); Anal. Calcd. for $C_{19}H_{20}O_3$: C, 76.99; H, 6.81. Found: C, 77.16; H, 6.41.

2,2-Dimethyl-1,7-dioxaspiro[4.4]nonane (9) and **2,2-Diphenyl-1,7-dioxaspiro[4.4]nonane (10)**[16]

To a solution of **44** (20 mg, 0.12 mmol) and Et_3SiH (28 μL, 0.18 mmol) in CH_2Cl_2 (2 mL) at -78℃ was slowly added BF_3•Et_2O (17 μL, 0.14 mmol). After 3h, a saturated $NaHCO_3$ solution (0.3 mL) was introduced, and the cooling bath was removed and the solution allowed to warm to rt with vigorous stirring. The mixture was diluted with ether (30 mL), the organic layer was separated, and washed with 10% $NaHCO_3$ (5 mL) and brine (10 mL). Concentration under reduced pressure and chromatography of the residue on silica gel (elution with dichloromethane-ethyl acetate, 5:1) afforded 9.1 mg (50%) of **9** as a low-boiling colorless liquid: ^{1}H NMR ($CDCl_3$) δ 1.20 (2s, 6H), 1.71-1.85 (m, 3H), 1.95-2.05 (m, 3H), 3.58-3.60 (ABq, *J*=8.8 Hz, 2H), 3.81-3.92 (m, 2H); ^{13}C NMR (C_6D_6) δ 29.2(2), 35.8, 39.1, 40.6, 67.8, 78.6, 80.7, 89.4; MS *m/z* 156 (M^+, 2.12); Anal. Calcd. for $C_9H_{16}O_2$: C, 69.18; H, 10.32. Found: C, 70.16; H, 9.19 (low boiling liquid).

The similar procedure was repeated using a solution of **45** (40 mg, 0.13 mmol) in CH_2Cl_2 (7 mL), Et_3SiH (64 μL, 0.4 mmol) and TFA (31 μL, 0.4 mmol) to afford, after chromatography on silica gel (elution with hexanes-ethyl acetate, 3:1), 30 mg (82%) of **10** as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.86-1.91 (m, 1H), 1.97-2.16 (m, 2H), 2.20-2.28 (m, 1H), 2.64-2.70 (m, 2H), 3.62-3.92 (ABq, *J*=9.0 Hz, 2H), 3.90-3.98 (m, 1H), 4.02-4.08 (m, 1H), 7.19-7.35 (m, 6H), 7.41-7.50 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 34.9, 39.2, 39.6, 67.9, 77.5, 88.4, 90.1, 125.8, 126.6, 128.1, 147.2; MS *m/z* 280 (M^+, 5.32); Anal. Calcd. for $C_{19}H_{20}O_2$: C, 81.38; H, 7.19. Found: C, 81.71; H, 7.04.

8-Phenylsulfenyl-2,2-diphenyl-1,7-dioxaspiro[4.4]nonane (46)[25]

A solution of **45** (126 mg, 0.43 mmol), thiophenol (88 μL, 1.28 mmol), and TFA (6.5 μL, 0.09 mmol) in CH_2Cl_2 (7 mL) was stirred for 15h at rt. The solution was diluted with CH_2Cl_2 (40 mL) and washed with 5% Na_2CO_3 (2x10 mL), and brine (2x20 mL). Concentration and chromatography of the residue on silica gel (elution with hexanes-ethyl acetate, 7:1) afforded 132 mg (80%) of **46** as a 1:1 separable diastereomers.

Higher R_f isomer as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.95-2.10 (m, 2H), 2.40 (d, *J*=7.6 Hz, 2H), 2.60-2.72 (m, 2H), 3.62-4.25 (ABq, *J*=8.8 Hz, 2H), 5.62 (t, *J*=7.6 Hz, 1H), 7.20-7.35 (m, 9H), 7.42-7.56

(m, 6H); ^{13}C NMR ($CDCl_3$) δ 36.8, 38.9, 45.7, 75.6, 87.1, 88.3, 88.4, 125.7, 125.8, 126.8, 126.9, 128.2, 128.8, 131.2, 146.6; HRMS: *m/z* (M^+) calcd for $C_{25}H_{24}O_2S$ 388.1498; found: 388.1476.

Lower R_f isomer as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 2.01-2.10 (m, 3H), 2.65-2.78 (m, 3H), 3.89-4.02 (ABq, *J*=9.4 Hz, 2H), 5.86 (t, *J*=6.9 Hz, 1H), 7.20-7.35 (m, 11H), 7.38-7.58 (m, 4H); Anal. Calcd. for $C_{25}H_{24}O_2S$: C, 77.29; H, 6.23. Found: C, 77.47; H, 6.20.

8-Phenylsulfinyl-2,2-diphenyl-1,7-dioxaspiro[4.4]nonane (47)[25]

To a solution of **46** (79 mg, 0.2 mmol) in CH_2Cl_2 (5 mL) at 0℃ was added a solution of *m*-CPBA (42 mg, 0.24 mmol) in CH_2Cl_2 (1.5 mL). After 1h, the mixture was diluted with CH_2Cl_2 (50 mL), washed with 5% Na_2CO_3 (2x10 mL), and brine (2x20 mL). Concentration and chromatography of the residue on silica gel (elution with hexanes-ethyl acetate, 1:1) afforded 70 mg (84%) of a diastereomeric mixture **47** as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 2.05-2.18 (m, 3H), 2.60-2.71 (m, 2H), 3.05-3.15 (dd, *J* =4.1, 7.4 Hz, 1H), 3.70-4.12 (ABq, *J*=8.8 Hz, 2H), 4.65-4.72 (m, 1H), 7.25-7.61 (m, 12H), 7.62-7.71 (m, 3H). Compound **47** was used immediately in the next step without further purification and characterization.

2,2-Diphenyl-1,7-dioxaspiro[4.4]non-8-ene (11)[25]

A solution of **47** (30 mg, 0.074 mmol) and triethyl phosphite (64.5 μL, 0.04 mmol) in toluene (7 mL) was refluxed for 2h under N_2. Concentration and chromatography of the residue on silica gel (elution with hexanes-ethyl acetate, 10:1) afforded 11.5 mg (55%) of **11** as a white solid: mp 104-105℃; ^{1}H NMR ($CDCl_3$) δ 2.01-2.15 (m, 2H), 2.64 (t, *J*=7.0 Hz, 2H), 4.01-4.45 (ABq, *J*=10.5 Hz, 2H), 5.09 (s, 1H), 6.55 (s, 1H), 7.19-7.30 (m, 7H), 7.40-7.49 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 36.8, 39.2, 80.5, 88.2, 92.3, 106.2, 125.8, 125.9, 126.7, 126.8, 128.0, 128.1, 147.1, 149.1; MS *m/z* 278 (M^+, 15.50); Anal. Calcd. for $C_{19}H_{18}O_2$: C, 81.97; H, 6.52. Found: C, 82.29; H, 6.61.

7-(1,3-Dioxolan-2-yl)-15,16-epoxy-8α-labda-13(16),14-dien-9α-ol (48)[29]

A mixture of hispanolone (**1**) (6 g, 18.86 mmol), ethylene glycol (10.52 mL, 188.67 mmol) and a catalytic amount of PTS (0.07 g, 0.38 mmol) in benzene (80 mL) was refluxed for 6h using a Dean-Stark apparatus. The mixture was diluted with ether (100 mL), and washed with 5% Na_2CO_3 (2x20 mL), and brine (2x50 mL). Concentration and chromatography of the residue on silica gel (elution with hexanes-ethyl acetate, 4:1) afforded 6.5 g (95%) of **48** as a colorless oil: $[\alpha]_D^{23}$ 0.24°($CHCl_3$; *c* 5.18); ^{1}H NMR (acetone-d_6) δ 0.85 (s, 3H), 0.87 (s, 3H), 0.90 (s, 3H), 0.93 (d, *J*=6.8 Hz, 3H), 1.11-1.20 (m, 1H), 1.40-1.75 (m, 9H), 1.90-2.01 (m, 1H), 2.07 (q, *J*=6.8 Hz, 1H), 2.50 (t, *J*=8.4 Hz, 2H), 3.85-3.96 (m, 4H), 3.23 (s, 1H), 6.33 (s, 1H), 7.29 (s, 1H), 7.39 (s, 1H); ^{13}C NMR (acetone-d_6) δ 7.1, 15.7, 18.7, 21.5, 21.6, 31.6, 31.7, 32.9, 33.1, 34.9, 41.9, 43.5, 43.6, 43.9, 64.1, 65.5, 77.4, 111.2, 111.4, 126.5, 138.6, 142.7; MS *m/z* 362 (M^+, 52.1); Anal. Calcd. for $C_{22}H_{34}O_4$: C, 72.87; H, 9.45. Found: C, 73.38; H, 9.86.

7-(1,3-Dioxolan-2-yl)-9α-trimethylsiloxy-15-trimethylsilyl-15,16-epoxy-8α-labda-13(16),14-diene (49) and 7-(1,3-Dioxolan-2-yl)-9α-trimethylsiloxy-16-trimethylsilyl-15,16-epoxy-8α-labda-13(16),14-diene (50)

The procedure described for the preparation of **31** was repeated using a mixture of TMEDA (3.46 mL, 24.30 mmol) and *n*-BuLi in hexane (17.36 mL, 1.4M, 24.30 mmol), a solution of **48** (6 g, 11.04 mmol) in dry ether (20 mL) and TMSCl (3.5 mL, 27.6 mmol) to afford, after chromatography on silica gel (elution with hexanes-ethyl acetate, 14:0.5) 4.66 g (82%) of **49** and **50** as a 2:1 inseparable mixture.

Data for **49**: A colorless oil: ^{1}H NMR (acetone-d_6) δ 0.15 (s, 9H), 0.30 (s, 9H), 0.86 (s, 3H), 0.88 (s, 3H), 0.94 (d, *J*=6.7 Hz, 3H), 1.09 (s, 3H), 1.30-1.50 (m, 4H), 1.52-1.85 (m, 6H), 1.90-2.01 (m, 1H), 2.25

(q, *J*=6.7 Hz, 1H), 2.45-2.60 (m, 2H), 3.72-3.80 (m, 1H), 3.87-4.01 (m, 3H), 6.60 (s, 1H), 7.51 (s, 1H); ^{13}C NMR (acetone-d_6) δ -2.07(3), 3.01(3), 8.2(2), 17.7, 18.9, 21.9, 22.4, 31.6, 32.2, 32.8, 33.9, 37.5, 41.8, 42.0, 42.5, 44.0, 63.7, 65.1, 85.5, 111.3, 121.1, 126.0, 142.9; MS *m/z* 506 (M^+-1, 0.07).

Data for **50**: A colorless oil: ^{1}H NMR (acetone-d_6) δ 0.30 (s, 9H), 0.41 (s, 9H), 0.90 (s, 3H), 0.91 (s, 3H), 0.98 (d, *J*=6.7 Hz, 3H), 1.12 (s, 3H), 1.30-1.50 (m, 4H), 1.52-1.85 (m, 6H), 1.90-2.01 (m, 1H), 2.25 (q, *J*=6.7 Hz, 1H), 2.45-2.60 (m, 2H), 3.72-3.80 (m, 1H), 3.87-4.01 (m, 3H), 6.36 (s, 1H), 7.62 (s, 1H); ^{13}C NMR (acetone-d_6) δ -2.07(3), 3.01(3), 8.3(2), 17.7, 19.4, 21.9, 22.4, 23.3, 31.6, 32.2, 33.3, 33.9, 38.4, 42.0, 42.5, 44.0, 63.7, 65.1, 85.5, 110.7, 136.1, 146.6, 153.9.

Anal. Calcd. for $C_{28}H_{50}O_4Si_2$: C, 66.35; H, 9.94. Found: C, 66.67; H, 10.50.

7-(1,3-Dioxolan-2-yl)-9α-trimethylsiloxy-15,16-epoxy-8α-labd-13(14)-en-15-one (51) and **7-(1,3-Dioxolan-2-yl)-9α-trimethylsiloxy-15,16-epoxy-8α-labd-13(14)-en-16-one (52)**

The procedure described for the preparation of **15** was repeated using a mixture of 32% peracetic acid (1.45 mL, 21.6 mmol) and powdered anhydrous NaOAc (1.77 g, 21.6 mmol) in CH_2Cl_2 (10 mL) as well as a solution of a mixture of **49** and **50** (2.74 g, 5.4 mmol) in CH_2Cl_2 (5 mL) to afford, after chromatography on silica gel (elution with hexanes-ethyl acetate, 4:1), 0.7 g (51%, 1.2 g of starting material was recovered) of **51** and 0.45 g (33%) of **52**, respectively.

Higher R_f isomer **52** as a colorless oil: $[\alpha]_D^{23}$ -3.72° ($CHCl_3$; *c* 11.25); ^{1}H NMR ($CDCl_3$) δ 0.12 (s, 9H), 0.77 (s, 3H), 0.78 (s, 3H), 0.80 (d, *J*=6.7 Hz, 3H), 0.94 (s, 3H), 1.25-1.79 (m, 11H), 1.89-2.01 (m, 1H), 2.08 (q, *J*=6.7 Hz, 1H), 2.29-2.38 (m, 1H), 3.71-3.80 (m, 1H), 3.85-3.95 (m, 3H), 4.68 (s, 2H), 7.01 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 3.14(3), 7.9(2), 17.7, 18.5, 21.9, 23.0, 31.9, 32.6, 33.3, 33.4, 33.9, 41.5, 42.1, 43.7, 63.4, 64.8, 69.9, 84.7, 111.1, 134.7, 143.3, 173.7; MS *m/z* 450 (M^+, 0.09); Anal. Calcd. for $C_{25}H_{42}O_5Si$: C, 66.62; H, 9.39. Found: C, 67.24; H, 9.94.

Lower R_f isomer **51** as a colorless oil: $[\alpha]_D^{25}$ -0.23° ($CHCl_3$; *c* 17.0); ^{1}H NMR ($CDCl_3$) δ 0.10 (s, 9H), 0.80 (s, 3H), 0.82 (s, 3H), 0.83 (d, *J*=6.7 Hz, 3H), 0.97 (s, 3H), 1.10-1.19 (m, 1H), 1.25-1.79 (m, 9H), 1.90-2.01 (m, 1H), 2.10 (q, *J*=6.7 Hz, 1H), 2.30-2.42 (m, 2H), 3.71-3.81 (m, 1H), 3.85-3.95 (m, 3H), 4.69 (s, 2H), 5.79 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 3.34(3), 8.2, 17.9, 18.6, 22.0, 26.3, 32.0, 32.8, 33.4, 33.5, 33.6, 41.5, 41.8, 42.2, 43.9, 63.8, 65.0, 72.9, 84.7, 111.1, 115.0, 170.3, 173.6; MS *m/z* 450 (M^+, 0.14); Anal. Calcd. for $C_{25}H_{42}O_5Si$: C, 66.62; H, 9.39. Found: C, 66.55; H, 9.38.

7-(1,3-Dioxolan-2-yl)-9α-hydroxy-15,16-epoxy-8α-labd-13(14)-en-15-one (53)[30]

To a solution of **51** (660 mg, 1.46 mmol) in CH_2Cl_2 (17 mL) at -10°C was added BF_3•Et_2O (0.27 mL, 2.19 mmol). After 1h, Et_3N (0.38 mL) was introduced. The mixture was diluted with CH_2Cl_2 (100 mL), and washed with brine (2x30 mL). Concentration and chromatography of the residue on silica gel (elution with hexanes-ethyl acetate, 2:1) afforded 524 mg (95%) of **53** as a colorless solid: mp 140-141°C; $[\alpha]_D^{25}$ 10.90° ($CDCl_3$; *c* 5.0); ^{1}H NMR ($CDCl_3$) δ 0.80 (s, 3H), 0.84 (s, 3H), 0.88 (s, 3H), 0.91 (d, *J*= 7.0 Hz, 3H), 1.19-1.70 (m, 9H), 1.95-2.05 (m, 3H), 2.46 (t, *J*= 8.0 Hz, 2H), 3.22 (s, 1H), 3.88-3.97 (m, 4H), 4.72 (t, *J*= 2.0 Hz, 2H), 5.76 (t, *J*=1.7 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 7.31, 15.8, 18.5, 21.8, 25.2, 31.4, 31.5, 31.6, 32.9, 33.2, 41.6, 43.4, 43.6, 43.9, 64.2, 65.4, 73.3, 76.5, 111.3, 114.8, 172.0, 174.2; Anal. Calcd. for $C_{22}H_{34}O_5$: C, 69.89; H, 9.06. Found: C, 69.70; H, 9.00.

(13*S*)-7-(1,3-Dioxolan-2-yl)-9α,13;15,16-diepoxy-8α-labdan-15-one (54) and **(13*R*)-7-(1,3-Dioxolan-2-yl)-9α,13;15,16-diepoxy-8α-labdan-15-one (55)**[26]

To a solution of **53** (268 mg, 0.71 mmol) in Et_3N (5 mL) was added DBN (0.2 mL) at rt. After 6h,

concentration under reduced pressure and chromatography of the residue on silica gel (elution with dichloromethane-ethyl acetate, 8:1) afforded 126 mg (47%) of **55** and 129 mg (48%) of **54**.

Higher R_f isomer **55** as a colorless oil: $[\alpha]_D^{24}$ -14.3° ($CDCl_3$; *c* 4.60); ^1H NMR ($CDCl_3$) δ 0.66 (s, 3H), 0.82 (d, *J*= 6.5 Hz, 3H), 0.85 (s, 3H), 0.92 (s, 3H), 1.18-1.55 (m, 6H), 1.69-1.84 (m, 3H), 1.95-2.12 (m, 4H), 2.16-3.01 (ABq, *J*= 17.1 Hz, 2H), 3.70-3.81 (m, 1H), 3.89-4.01 (m, 4H), 4.12-4.45 (ABq, *J*= 9.0 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 8.0, 17.2, 18.5, 21.9, 30.7, 31.7, 32.7, 32.8, 33.0, 38.7, 41.6, 42.2, 42.9, 43.4, 43.5, 63.9, 65.4, 78.9, 86.4, 95.0, 110.7, 174.5; MS *m/z* 378 (M^+, 4.07); Anal. Calcd. for $C_{22}H_{34}O_4$: C, 69.89; H, 9.06. Found: C, 69.83; H, 9.33.

Lower R_f isomer **54** as a colorless oil: $[\alpha]_D^{24}$ 20.6° ($CDCl_3$; *c* 4.35); ^1H NMR ($CDCl_3$) δ 0.80 (s, 3H), 0.87 (d, *J*= 6.5 Hz, 3H), 0.89 (s, 3H), 0.94 (s, 3H), 1.15-1.20 (m, 2H), 1.34-1.58 (m, 5H), 1.60-1.70 (m, 3H), 2.02-2.54 (m, 4H), 2.47-3.16 (ABq, *J*=17.3 Hz, 2H), 3.75-3.85 (m, 1H), 3.92-4.01 (m, 3H), 4.03-4.35 (ABq, *J*= 8.5 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 8.3, 17.1, 18.5, 22.0, 30.8, 31.8, 32.4, 32.8, 33.1, 38.7, 41.7, 42.2, 42.4, 43.8, 64.0, 65.5, 76.5, 78.4, 88.6, 95.0, 110.7, 174.6; MS *m/z* 378 (M^+, 4.51); Anal. Calcd. for $C_{22}H_{34}O_4$: C, 69.89; H, 9.06. Found: C, 69.67; H, 9.27.

(13*S*)-7-(Dioxolan-2-yl)-9α,13;15,16-diepoxy-8α-labdan-15α-ol (56) and **(13*S*)-7α-Hydroxyethoxy-9α,13;15,16-diepoxy-8α-labdan-15β-ol (57)**

The procedure described for the preparation of **44** was repeated using a mixture of **54** (176 mg, 0.46 mmol) in CH_2Cl_2 (7 mL) and DIBAL in hexane (0.93 mL, 1M, 0.93 mmol) to afford, after chromatography on silica gel (elution with hexanes-ethyl acetate, 1:1), 115 mg (66%) of **56** and 44 mg (25%) of **57**.

Higher R_f isomer **56** as a colorless oil: ^1H NMR ($CDCl_3$) δ 0.78 (s, 3H), 0.83 (s, 3H), 0.92 (s, 3H), 0.98 (d, *J* =6.7 Hz, 3H), 1.12-1.58 (m, 7H), 1.69-1.95 (m, 7H), 2.08 (q, *J* =6.7 Hz, 1H), 2.37 (d, *J* =13 Hz, 1H), 3.64-4.29 (ABq, *J* =8.9 Hz, 2H), 3.70-3.79 (m, 1H), 3.81-3.96 (m, 3H), 5.31-5.40 (m, 1H), 5.62-5.70 (br d, *J*=11 Hz, OH, 1H); ^{13}C NMR ($CDCl_3$) δ 9.0, 17.7, 18.6, 21.8, 29.3, 31.6, 31.9, 32.7, 32.9, 33.5, 41.6, 42.2, 42.6, 42.7, 44.9, 64.1, 64.8, 76.5, 90.0, 95.2, 99.3, 111.3; Anal. Calcd. for $C_{22}H_{36}O_5$: C, 69.43; H, 9.54. Found: C, 68.75; H, 9.54.

Lower R_f isomer **57** as a colorless solid: mp 147-148°C; ^1H NMR ($CDCl_3$) δ 0.80 (s, 3H), 0.83 (s, 3H), 0.92 (s, 3H), 1.13 (d, *J* =7.0 Hz, 3H), 1.22-1.55 (m, 6H), 1.70-1.92 (m, 8H), 2.45 (d, *J* =10.8 Hz, 1H), 3.22 (q, *J* =7.0 Hz, 1H), 3.30-3.39 (m, 1H), 3.50-3.61 (m, 2H), 3.66 (d, *J* =9.0 Hz, 1H), 3.69-3.78 (m, 1H), 4.33 (d, *J* =9.0 Hz, 1H), 5.35-5.42 (m, 1H), 6.23-6.31 (br d, *J* =12 Hz, OH, 1H); ^{13}C NMR ($CDCl_3$) δ 14.4, 17.7, 18.6, 21.9, 25.2, 29.2, 31.2, 32.9, 33.5, 38.4, 39.8, 41.6, 43.0, 44.3, 62.2, 72.9, 80.8, 90.2, 94.7, 99.2; Anal. Calcd. for $C_{22}H_{38}O_5$: C, 69.06; H, 10.02. Found: C, 68.90; H, 9.99. For the single crystal X-ray structure determination of **57**, see the communication.[1a]

(13*S*)-9α,13;15,16-Diepoxy-8α-labdan-7-one (4)

The procedure described for the preparation of **9** was repeated using a mixture of **56** (10 mg, 0.03 mmol) in CH_2Cl_2 (1 mL), Et_3SiH (14 μL, 0.09 mmol) and $BF_3{\cdot}Et_2O$ (5.5 μL, 0.05 mmol) to afford, after chromatography on silica gel (elution with hexanes-ethyl acetate, 1:1), 6 mg (72%) of **4** as a colorless oil: $[\alpha]_D^{27}$ -111° ($CDCl_3$; *c* 0.18); ^1H NMR ($CDCl_3$) δ 0.87 (s, 6H), 1.06 (d, *J*=6.5 Hz, 3H), 1.12 (s, 3H), 1.20-1.31 (m, 3H), 1.42-1.59 (m, 3H), 1.85-1.93 (m, 3H), 1.97-2.04 (m, 2H), 2.15-2.30 (m, 3H), 2.35-2.49 (m, 1H), 2.72 (q, *J*=6.5 Hz, 1H), 3.51-3.68 (ABq, *J*=8.4 Hz, 2H), 3.79-3.90 (m, 2H); ^{13}C NMR ($CDCl_3$) δ

8.74, 17.21, 18.13, 20.73, 29.10, 29.29, 32.12, 33.18, 37.63, 38.64, 39.76, 41.18, 42.36, 46.47, 50.01, 66.92, 77.32, 90.65, 95.94, 210.20; HRMS: *m/z* (M^+) calcd for $C_{20}H_{32}O_3$ 320.2353; found: 320.2347.

(13*R*)-7-(1,3-Dioxolan-2-yl)-9α,13;15,16-diepoxy-8α-labdan-15-ol (58)

The procedure described for the preparation of **44** was repeated using a mixture of **55** (150 mg, 0.40 mmol) in CH_2Cl_2 (5 mL) and DIBAL in hexane (0.79 mL, 1M, 0.79 mmol) to afford, after chromatography on silica gel (elution with hexanes-ethyl acetate, 1:1), 105 mg (70%) of **58** as a colorless oil, which consisted of a 1:1 mixture of diastereomers of **58**: ^{1}H NMR ($CDCl_3$) (**A** isomer) δ 0.77 (s, 3H), 0.82 (s, 3H), 0.89 (d, *J*=6.8 Hz, 3H), 0.92 (s, 3H), 1.10-1.21 (m, 2H), 1.32-1.50 (m, 6H), 1.68-1.75 (m, 2H), 1.85-2.15 (m, 5H), 2.33 (d, *J*=13 Hz, 1H), 3.59-4.30 (ABq, *J*=8.9 Hz, 2H), 3.69-3.75 (m, 1H), 3.85-4.12 (m, 4H), 5.37-5.55 (m, 1H); (**B** isomer), most of other signals partially overlap with those of isomer **A**; ^{13}C NMR ($CDCl_3$) (most carbons show two peaks because of diastereomerism) δ 8.1, 8.5, 17.2, 17.4, 18.6, 21.8, 22.0, 31.3, 31.9, 32.6, 32.8, 32.9, 33.1, 33.5, 34.1, 39.6, 41.8, 42.5, 43.1, 43.6, 43.8, 45.4, 47.8, 64.0, 65.1, 65.5, 78.6, 90.2, 93.4, 95.1, 99.1, 99.5, 110.8; HRMS: *m/z* (M^+-C_2H_5) calcd for $C_{20}H_{31}O_5$ 351.2173; found: 351.2173.

(13*R*)-9α,13;15,16-Diepoxy-8α-labdan-7-one (3)

The procedure described for the preparation of **9** was repeated using a mixture of **58** (28 mg, 0.07 mmol), Et_3SiH (47 μL, 0.29 mmol) in CH_2Cl_2 (3 mL) and BF_3•Et_2O (13.5 μL, 0.11 mmol) to afford, after chromatography on silica gel (elution with hexanes-ethyl acetate, 2:1), 15 mg (64%) of **3** as a colorless oil: $[\alpha]_D^{27}$ -32.18°($CHCl_3$; *c* 0.72),{lit[1d] $[\alpha]_D^{22}$ -33.6°($CDCl_3$; *c* 0.60)}; ^{1}H NMR ($CDCl_3$) δ 0.87 (s, 6H), 0.99 (d, *J*=6.5 Hz, 3H), 1.13 (s, 3H), 1.21-1.30 (m, 1H), 1.41-1.69 (m, 6H), 1.85-2.01 (m, 4H), 2.02-2.30 (m, 3H), 2.35-2.45 (m, 1H), 2.69 (q, *J*=6.5 Hz, 1H), 3.58-3.75 (ABq, *J*= 8.6 Hz, 2H), 3.79-3.94 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 9.07, 17.76, 18.72, 21.27, 29.74, 32.72, 32.90, 33.69, 38.12, 39.15, 40.68, 41.83, 42.86, 46.69, 50.44, 67.70, 76.48, 91.23, 96.45, 210.66; HRMS: *m/z* (M^+) calcd for $C_{20}H_{32}O_3$ 320.2353; found: 320.2351.

(13*R*)-15-Phenylsulfenyl-9α,13;15,16-diepoxy-8α-labdan-7-one (59) and **(13*R*)-15-Hydroxy-9α,13;15,16-diepoxy-8α-labdan-7-one (60)**

The procedure described for the preparation of **46** was repeated using a mixture of **58** (153 mg, 0.40 mmol), thiophenol (84 μL, 1.21 mmol), and TFA (6 μL, 0.08 mmol) in CH_2Cl_2 (8 mL) to afford, after chromatography on silica gel (elution with hexanes-ethyl acetate, 3:1), 47 mg (30%) of **59**, 34 mg (25%) of **60** and 52 mg of a mixture of di- and mono-sulfides, respectively.

Higher R_f isomers were a mixture of di- and mono-sulfides.

Middle R_f isomer **59** as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 0.87 (s, 3H), 0.89 (s, 3H), 1.06 (d, *J*=6.6 Hz, 3H), 1.13 (s, 3H), 1.21-1.60 (m, 7H), 1.91-2.42 (m, 8H), 2.67 (q, *J*=6.6 Hz, 1H), 3.59-4.01 (ABq, *J*=8.5 Hz, 2H), 5.50 (t, *J*=7.3 Hz, 1H), 7.22-7.38 (m, 3H), 7.45-7.52 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 8.9, 17.7, 18.7, 21.3, 29.5, 32.7, 32.9, 33.7, 38.5, 39.1, 41.7, 46.2, 46.5, 50.3, 75.6, 86.6, 89.6, 96.4, 127.0, 128.8, 131.2, 135.8, 210.5; Anal. Calcd. for $C_{26}H_{36}O_3S$: C, 72.86; H, 8.47. Found: C, 72.61; H, 8.56.

Lower R_f isomer **60** as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 0.86 (s, 3H), 0.86 (s, 3H), 0.96 (d, *J*=6.6 Hz, 3H), 1.12 (s, 3H), 1.20-1.69 (m, 6H), 1.85-1.92 (m, 2H), 2.01-2.45 (m, 5H), 2.66 (q, *J*=6.6 Hz, 1H), 3.56-3.91 (ABq, *J*=8.1 Hz, 2H), 3.65-3.75 (m, 3H), 5.08-5.15 (m, 1H); ^{13}C ($CDCl_3$) δ 8.9, 17.7, 18.7, 21.3, 29.5, 32.7, 33.6, 39.15, 41.7, 42.9, 46.4, 46.8, 50.2, 62.3, 70.4, 75.5, 90.0, 96.3, 104.4, 210.6 (most carbons show two peaks because of diastereomerism); HRMS: *m/z* (M^+) calcd for $C_{20}H_{32}O_4$ 336.2302; found: 336.2319.

The procedure described for the preparation of **59** was repeated using **60** (60 mg, 0.18 mmol) in CH_2Cl_2 (3 mL), thiophenol (37 μL, 0.54 mmol) and TFA (2.7 μL, 0.04 mmol) to afford, after chromatography on silica gel (elution with hexanes-ethyl acetate, 3:1), 34 mg (50%) of **59**. The physical and spectroscopic data of **59** are identical with an authentic sample prepared previously.

(13*R*)-15-Phenylsulfinyl-9α,13;15,16-diepoxy-8α-labdan-7-one (61)[31]

To a solution of **59** (15 mg, 0.04 mmol) in MeOH (2 mL) at 0℃ was added a solution of 0.5 M $NaIO_4$ (78 μL, 0.04 mmol). After the mixture was stirred at 0℃ for 5h, the precipitated $NaIO_3$ was removed by filtration, and the filtrate was diluted with $CHCl_3$ (40 mL). The organic layer was washed with 5% $NaHCO_3$ (2x10 mL) and brine (3x10 mL). Concentration under reduced pressure and chromatography of the residue on silica gel (elution with hexanes-ethyl acetate, 5:1) afforded 10.5 mg (67%) of **61** as a colorless oil: Compound **61** was used immediately in the next step without further purification and characterization.

(13*R*)-9α,13;15,16-Diepoxy-8α-labd-14-en-7-one (2)

The procedure described for the preparation of **11** was repeated using a mixture of **61** (14 mg, 0.04 mmol) and triethyl phosphite (24 μL, 0.14 mmol) in toluene (5 mL) to afford, after chromatography on silica gel (elution with hexanes-ethyl acetate, 7:1), 6.8 mg (61%) of **2** as a colorless oil: $[\alpha]_D^{25}$ -64.6° (C_6H_6; *c* 0.85),{lit[1d] $[\alpha]_D^{22}$ -63.6°(C_6H_6; *c* 0.55)}; ^{1}H NMR ($CDCl_3$) δ 0.86 (s, 6H), 0.99 (d, *J*=6.5 Hz, 3H), 1.11 (s, 3H), 1.25-1.65 (m, 6H), 1.75-2.15 (m, 4H), 2.15-2.40 (m, 3H), 2.69 (q, *J*=6.5 Hz, 1H), 4.02-4.41 (ABq, *J*=10.4 Hz, 2H), 5.13 (d, *J*=2.5 Hz, 1H), 6.42 (d, *J*=2.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 9.19, 17.30, 18.69, 21.29, 30.20, 32.54, 32.65, 37.94, 38.31, 39.06, 41.64, 42.49, 47.07, 50.72, 80.82, 93.78, 96.50, 107.05, 148.06, 210.41.

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