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Studies on the synthesis of (±)-pathylactone A, a nor-sesquiterpene lactone isolated from marine sources

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Abstract—An approach to the synthesis of a highly substituted carbon skeleton exhibited by some unusual nor-sesquiterpenes isolated from marine sources, is described. Our strategy was applied for the total synthesis of pathylactone A, which has now been prepared by an unambiguous route and found to be different from the natural product.

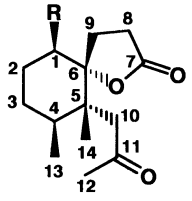
1. Introduction

Pathylactone A (**1**) is an unusual and densely substituted nor-sesquiterpene isolated by Su et al.,[1] in 1991 from the soft coral *Paralemnalia thyrsoides*, found in the South China Sea. They assigned the structure and relative stereochemistry depicted in Fig. 1, based on one- and two-dimensional NMR data.

A year later, Scheuer et al.[2] reported the isolation and chemical characterization of napalilactone (**2**), another example of this class of nor-sesquiterpene, from the soft coral *Lemnalia africana*.

The biological activity of these spirolactone nor-sesquiterpenes remains unknown, but their unusual and stereochemically complex structures make them challenging synthetic targets.

As part of a current research program directed towards the total synthesis of some marine natural products, we describe herein a study aimed at the total synthesis of (±)-pathylactone A (**1**). Our interest was focused on the development of a simple and straightforward method, which would allow us to prepare not only the natural product but some non-natural derivatives, directed towards the study of the biological profile of this kind of spirolactone nor-sesquiterpene.



R = OH, pathylactone-A (1)
R = Cl, napalilactone (2)

Figure 1. Structures of pathylactone A and napalilactone.

From our point of view, **1** could be prepared from the spiroether **3** through two sequential oxidation steps, e.g. Wacker oxidation of the allyl moiety and oxidation of the cyclic ether to furnish the spirolactone unit. The preparation of the spiroether moiety with the correct stereochemistry at C6 (pathylactone-A numeration, Scheme 1) could be secured by the regioselective opening of the epoxide **4**. The latter could be easily obtained by the epoxidation reaction of alkene **5**, which can be prepared by a regioselective dehydration reaction of a tertiary alcohol. The addition of a suitably functionalized organometallic reagent to α-allyl cyclohexenone **6** could furnish the tertiary alcohol necessary for the dehydration step (Scheme 1). The required ketone **6** could be stereoselectively prepared through a conjugate addition of lithium dimethylcuprate to the double bond of 2-methylcyclohexenone (**7**), followed by the trapping of the copper enolate intermediate with allyl bromide. The control of the relative stereochemistry of the methyl groups at C4 and C5 (pathylactone-A numeration) should be secured in this step (Scheme 1). Finally, ketone **7** could be easily prepared from methylcyclohexanol.

The only doubt concerning the stereochemical control of this strategy relies on the stereoselectivity obtained in the epoxidation step, although this has been proved not to be crucial. However, it would be important to us to separate these diastereoisomeric epoxides. We thought that the opening of the α-oriented epoxide with chloride ion as nucleophile could be used as a key step in the total synthesis

Keywords: pathylactone A; epi-pathylactone A; natural products; total synthesis.

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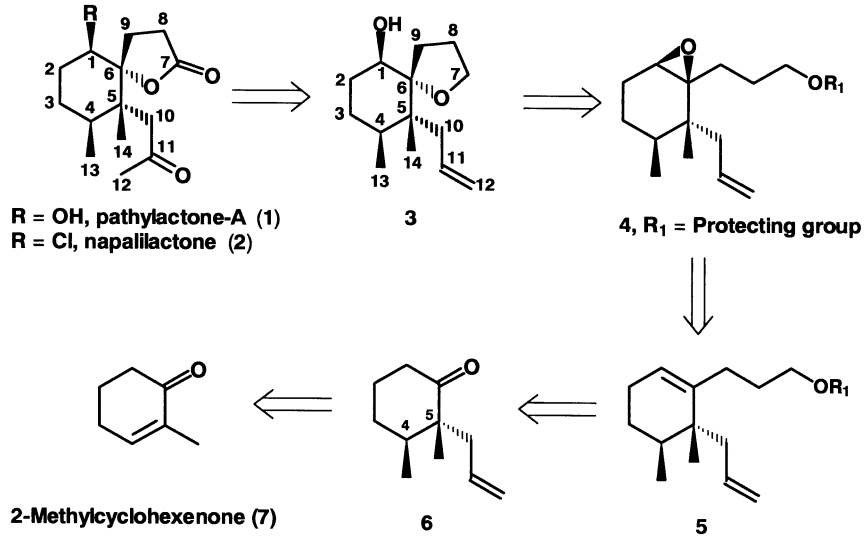


Scheme 1. Retrosynthesis for the preparation of pathylactone A.

of napalilactone (**2**, Scheme 1), while the β-oriented isomer could be used as a substrate in the total synthesis of pathylactone A, as depicted in Fig. 2. According to the Baldwin rules, the favored cyclization should preferentially lead to the spiro compound.[3] Depending on the success attained with this strategy, some additional modifications should allow us to synthesize **2**, in its racemic form.

2. Results and discussions

Our synthesis started with the preparation of the 2-methylcyclohexenone **7**, which was obtained using a standard procedure[4] in three steps and 73% overall yield from commercial 2-methylcyclohexanol.

To obtain the carbonyl compound **6** we decided to take advantage of the greater stereoselectivity and generally greater yields of 1,4-addition products obtained using organocopper reagents. Boeckman[5] has described a method based on a stereo- and regioselective double alkylation of α,β-unsaturated ketones. The 1,4-addition of lithium dimethylcuprate to 2-methylcyclohexenone,[5] followed by the regioselective alkylation of the copper enolate intermediate with allyl bromide, gave the allyl ketone **6a/b** (*cis*:*trans* 20:80), as a diastereoisomeric mixture (GC analysis), readily separated by column chromatography (Scheme 2). Although, Boeckman reported a diastereoselection ratio of 10:90 (*cis*:*trans*), we, as well as others,[6] were unable to reproduce this result.

We tried to confirm the stereochemical assignments of **6a/b** by NOE experiments, through the irradiation of the methyl group protons at C4 and C5.[7] Unfortunately, the results were not conclusive, mainly due to saturation of the methyl group protons at C4, when the C5 methyl group protons were irradiated, and vice versa.

To prepare the spiro γ-butyrolactone moiety at C6, it was necessary to add a suitably functionalized three carbon residue (fragment C7–C9) to ketone **6b**. This fragment could be readily obtained from 1,3-propanediol by using the method recently described by Forsyth et al.,[8] and Chen and Reamer.[9]

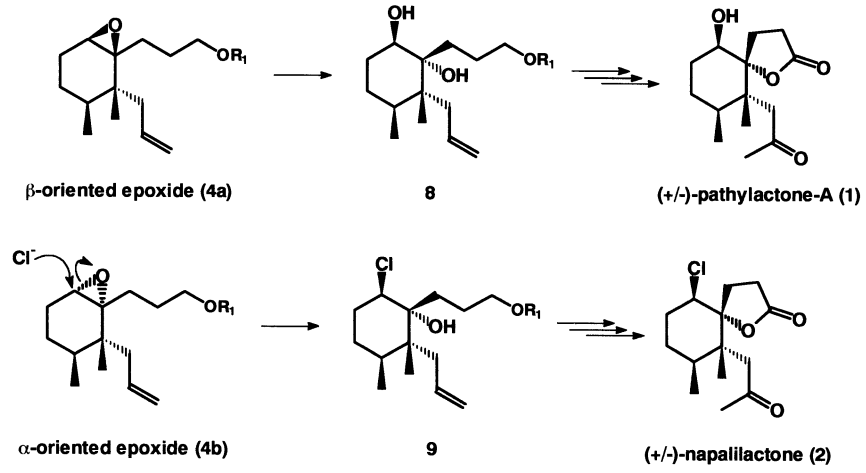
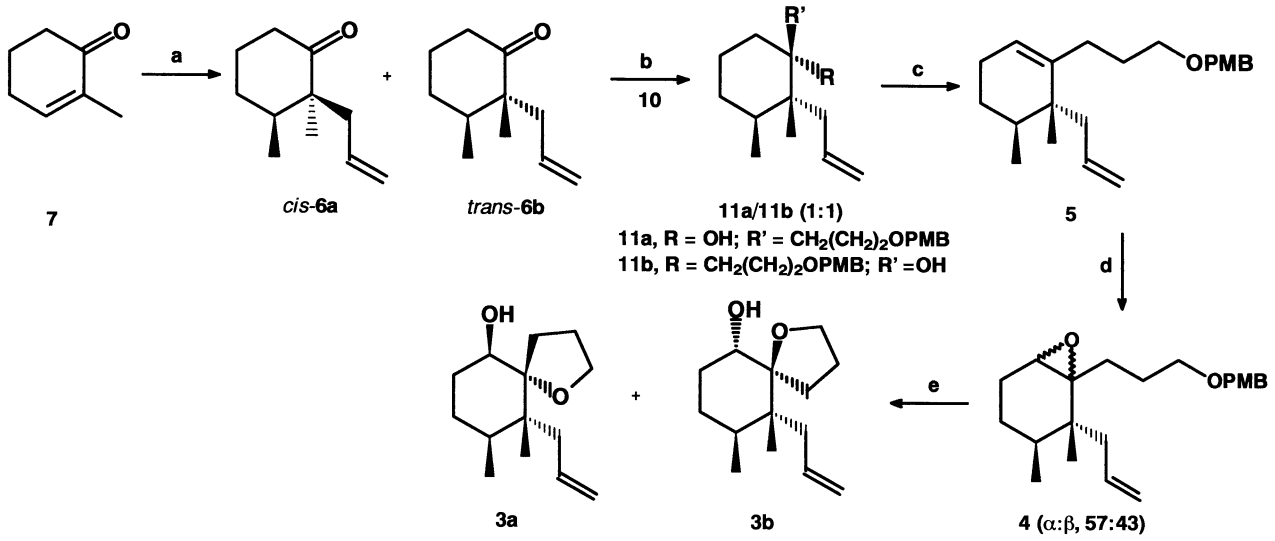


Figure 2. Preparation of **1** and **2** from diastereoisomeric epoxides.



Scheme 2. Preparation of the spiroethers **3a** and **b**. (a): (i) $(CH_3)_2CuLi$, ether, 0°C; (ii) DME, allyl bromide, rt, 15 min, (**6a/b**, 1:4), 77%; (b) $I(CH_2)_2CH_2OPMB$ (**10**), *t*-BuLi, ether, −23°C, 1 h, 92% (based on recovered starting material); (c) $POCl_3$, DBU, Py, rt, 24 h, 78%; (d) MCPBA, CH_2Cl_2, 0°C, 8 h, 88%; and (e) DDQ, CH_2Cl_2:H_2O (18:1), 3 h, 94%.

Thus, 1,3-propanediol was treated with sodium hydride in THF at 0°C, followed by addition of *p*-methoxybenzyl chloride to furnish, a PMB/ether alcohol intermediate, in 84% yield. The mesylation of the alcohol, followed by substitution with NaI, provided iodide **10**, in 98% yield for the two steps.

The ketone *trans*-**6b** was treated at −23°C with the organolithium compound derived from iodide **10** (generated in situ by treatment with an ethereal solution of *t*-butyllithium) to furnish the tertiary alcohol **11**, as a mixture of diastereoisomers (ratio **11a/b**; 50:50) (Scheme 2).[10]

The treatment of the mixture of alcohols **11a/b** with $POCl_3$/DBU in the presence of pyridine gave the alkene **5**, in 88% yield, contaminated with a trace of the exocyclic alkene, only detectable by gas chromatography (HP5 column, ≤5%). Thus, alkene **5** was treated with MCPBA in dichloromethane at 0°C, to provide regioselectively the α- and β-oriented epoxides **4a/b** in 82% yield, in a 57:43 mixture ratio (determined by analysis of the 500 MHz ^{1}H NMR spectrum).

We were unable to separate the diastereoisomeric epoxides **4a/b**, despite various attempts (preparative HPLC, column chromatography, preparative thin-layer chromatography). As we are interested in having some non-natural derivatives of these spirolactone sesquiterpenes, we decided to continue our synthesis with the mixture of epoxides.

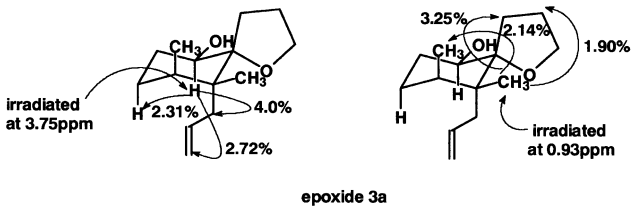


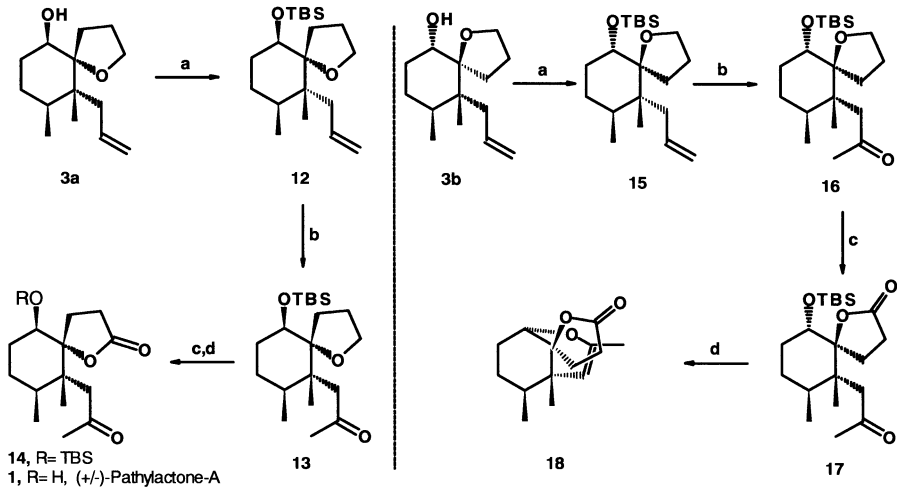
Figure 3. NOE experiments with spiroether **3a**.

The epoxides **4a/b** were treated with DDQ in a mixture of dichloromethane/water (18:1) in order to remove the PMB group. These conditions gave spiroethers **3a/b** in 94% yield. Most probably, formation of spiroethers **3a/b** arise due to a decrease of the pH of the reaction mixture when the quinone is reduced. There are other examples of this kind of cyclization reaction, in the literature, which are characterized by a high level of stereoselectivity.[8,11] Fortunately the spiroethers were readily separated by column chromatography (Scheme 2).

To have additional information about the stereochemical assignments of these compounds (**3a/b**), we decided to establish the relative stereochemistry by way of an NOESY experiment (Fig. 3). Irradiation of **3a** at 3.75 ppm (multiplet attributed to carbinolic hydrogen) showed an increment of 4.0 and 2.72% on signals at 5.0 and 5.99 ppm, attributed to the vinylic methylene and the olefinic methylene, respectively. An increase in the signal attributed to the axial hydrogen at C3 was also observed. Irradiation of the protons of the quaternary methyl group showed an increase in the absorption attributed to the C8, C9 and vicinal methyl group protons. When the same experiment was performed with the epoxide **3b**, we observed an increment only in methyl group protons. These results clearly indicated that the spiroether **3a** had the correct stereochemical arrangement for the preparation of **1**.

To finish the total synthesis of pathylactone A, it was necessary to oxidize the spiroether and the allyl moiety. To avoid problems with the secondary hydroxyl group at C1 during these oxidation steps, we first protected it as a TBS ether (Scheme 3). This reaction sequence was carried out separately on spiroethers **3a** and **b**.

Thus, treatment of **3a** or **b** with TBS triflate in the presence of triethylamine in dichloromethane gave the silyl ethers **12** and **15** in 94 and 92% yield, respectively. To avoid the removal of the silyl protecting group, a modified Wacker[12]



Scheme 3. Preparation of pathylactone A. (a) TBSTf, Et_3N, CH_2Cl_2, rt (94% for **12** and 92% for **14**); (b) $PdCl_2$, $Cu(OAc)_2$, *N*,*N*-dimethylacetamide/water (7:1), 50% (for **13** and **15**); (c) $RuCl_3.H_2O$ (10% aq. sol.), $NaIO_4$, AcOEt, rt, 23 h; and (d) HF, CH_3CN, rt, 3 h (76% for the two steps for **1** and **16**).

reaction was carried out, to give the corresponding methylketones (**13** and **16**) in 50% yield. Subsequent oxidation with $RuCl_3{\cdot}H_2O$ in the presence of $NaIO_4$ led to the spirolactones **14** and **17** in 84% yield for both cases. To remove the silyl group the spirolactone **14** was treated with a solution of HF (48% in water) to provide pathylactone A in 90%. When the spirolactone **17** was treated with HF in CH_3CN, ^1H NMR analysis revealed the formation of a different type of product. Some spectral features of this new compound drew our attention. First, the absorption at 2.46 ppm, attributed to methylene of the methylketone moiety disappeared. Associated to that was the disappearance of the carbonyl carbon absorption at 209.8 ppm. The absorption at 2.23 ppm attributed to methyl unit of the methylketone moiety, shifted to 1.75 ppm, associated with the appearance of an absorption at 4.12 ppm, which integrating to one hydrogen. The ^{13}C NMR spectrum showed an additional CH group and the disappearance of a CH_2. Analysis of the IR spectrum showed the disappearance of the ketone carbonyl absorption at 1712 cm^{-1} and the appearance of an absorption at 1778 cm^{-1}, confirming the presence of the spirolactone unity. All the spectral data is compatible with the structure proposed for **18**. The formation of this unusual structure is only possible if the hydroxyl group and the methylketone moiety were on the same face of the molecule. This result proves that compound **3b** has an α stereochemical arrangement at C1.

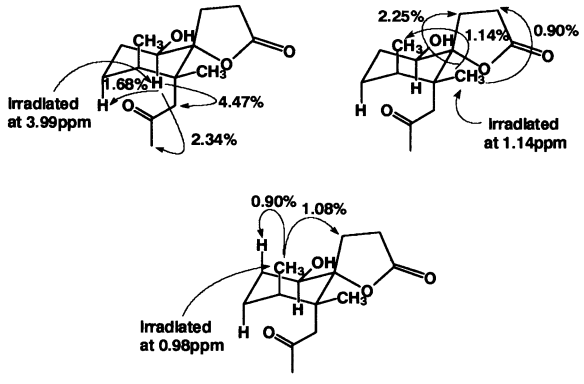


Figure 4. NOESY experiments with synthetic pathylactone A.

To confirm the relative stereochemistry of **1**, we carried out several NOESY experiments according to those described by Su et al.[1] Thus, we irradiated several hydrogens in order to observe the NOE effects in other points of the structure. The results are shown in Fig. 4. The incremental values observed in the NOESY experiments point out unambiguously that the relative stereochemistry of all stereocenters was correctly controlled and it was totally in accordance with that proposed by Su et al.[1]

With these data in hand, we carefully compared our spectral data (^1H and ^{13}C NMR) with those described by Su et al. However, to our surprise, NMR data of synthetic **1** shows some discrepancies with those described for the natural product, e.g. a singlet had been attributed to the methylene of the methylketone unit (C10, Scheme 1), in the synthetic product this methylene appears as two duplets centered at 2.77 ppm (J=15.5 Hz). The carbinolic proton in our product appeared at 3.99 ppm (double doublets, J=10.9 and 4.27 Hz), with two coupling constants, the major one clearly indicating that this proton was in an axial position, as proposed by Su et al.

The NMR data obtained by us for the synthetic pathylactone A did not match that published for the natural product. We tried to understand these discrepancies by performing a careful re-examination of all synthetic steps and the spectral data obtained for the intermediates, however all NOESY experiments indicated unambiguously that the relative stereochemistries of all stereocenters exhibited by the synthesized molecule were adequately controlled.

For the natural product the absorption of the carbinolic proton was attributed at 4.33 ppm. In the ^{13}C NMR of the natural product, the carbon at C1 appears at 63.7 ppm. Surprisingly, this carbon is shifted to downfield with a difference of almost 9 ppm from the synthetic product. The absorption value (^1H and ^{13}C NMR) found for the

Table 1. NMR spectral data for pathylactone A (natural and synthetic) and *epi*-pathylactone A (**20**)

Carbon No.	^{13}C NMR (100 MHz, $CDCl_3$)		^{1}H NMR (500 MHz, $CDCl_3$)		NMR (500 MHz, $CDCl_3$) for *epi*-pathylactone A (**20**)	
	Natural	Synthetic	Natural	Synthetic	^{13}C	^{1}H
1	63.7	71.1	4.33 (dd, *J*=10.9 and 3.9 Hz)	3.99 (dd, *J*=10.9 and 4.2 Hz)	65.0	4.27 (m, 1H)
2	28.6	27.0	1.90–2.06	1.60–1.90	27.0	1.78–2.0
3	26.7	25.7	1.44–1.80	1.44–1.78	26.0	1.44–1.79
4	33.0	33.7	2.39	2.41–2.33	33.7	2.38
5	45.9	45.1	–	–	45.3	–
6	91.8	93.1	–	–	92.0	–
7	175.5	177.3	–	–	177.0	–
8	29.1	29.4	2.50–2.65	2.46–2.71	29.0	2.48–2.67
9	24.5	23.4	2.32	2.21–2.33	24.0	2.30
10	46.6	47.6	2.69 (s)	2.77–2.69 (two doublet, *J*=15.5 Hz)	47.0	2.80–2.73 (two doublet, *J*=15.1 Hz)
11	207.6	208.7	–	–	207.0	–
12	32.6	32.9	2.10	2.17	32.2	2.09
13	15.4	15.9	0.94 (d, *J*=7.8 Hz)	0.98 (d, *J*=7.5 Hz)	15.9	0.96 (d, *J*=7.7 Hz)
14	17.7	17.2	1.12 (s)	1.14 (s)	17.2	1.12 (s)

The synthetic product is a solid melting at 43–45°C (the natural product melt at 44.5–47.0°C)[1]. *epi*-Pathylactone melting at 46–49°C. All the NMR spectra were recorded using an INOVA NMR equipment at 500 MHz for ^{1}H and 125 MHz for ^{13}C using $CDCl_3$ as solvent and TMS as internal standard.[1,15]

natural product could suggest that the hydroxyl group at C1 was not in an axial position, but in an equatorial one.

Under normal circumstances, a carbon bearing an equatorial hydroxyl group shows an absorption between 70–71 ppm,[13] which agrees with our synthetic product. In the natural product, this carbon apparently shows an unusual protection.

In Table 1, the NMR (^{1}H and ^{13}C) data for synthetic and natural pathylactone A are shown.

In order to propose an alternative structure for pathylactone A, based on the possibility of the hydroxyl bearing in an axial position, we prepared epimeric pathylactone A (at C1), as outlined in Scheme 4.

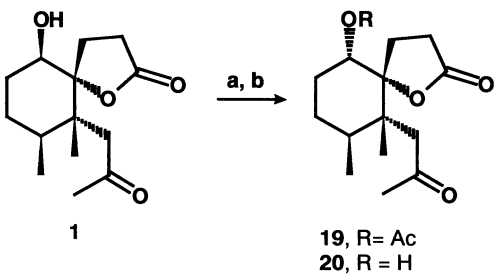
Mitsunobu reaction[16] with **1** furnished acetate **19** in 62% yield. The presence of some elimination product was also detected by gas chromatography (10–15%). All spectral data obtained for **19** were compatible with the structure. The acetate **19** was then treated with LiOH in a mixture THF/water to furnish *epi*-pathylactone A (**20**) in 68% yield.

The carbinolic proton in *epi*-pathylactone A (**20**) appeared at 4.27 ppm (as a multiplet), with two similar coupling constants (*J*=4.2 and 2.9 Hz), which is in agreement with a proton in an equatorial position (di-equatorial and axial-equatorial coupling constants).

All the data obtained from ^{1}H and ^{13}C NMR spectra (Table 1) were compatible for the structure of the synthetic *epi*-pathylactone A (**20**). When the absorption at 4.27 ppm, attributed to the equatorially oriented carbinolic proton, was irradiated, we observed NOE increments in axial hydrogens at C2, hydrogens of the methyl group at C4 and protons at C9 (Fig. 5). The spectral data for this non-natural compound showed some similarity to those described for natural pathylactone A, however the data obtained from the NOESY experiments were different from those described for the natural product.

These data pointed out clearly that the carbinolic proton was not in an equatorially position in the natural product.

Based on all data we have (^{1}H, ^{13}C NMR and NOESY experiments, MM2 calculations) for the synthetic products (pathylactone A and *epi*-pathylactone A), we believe that the structure proposed by Su is correct, but some ^{1}H and ^{13}C



Scheme 4. Preparation of *epi*-pathylactone A (**20**). (a) DEAD, PPh_3, AcOH, CH_2Cl_2, 3 h, 62%; and (b) LiOH, THF:H_2O (3:1), rt, 8 h, 68%.

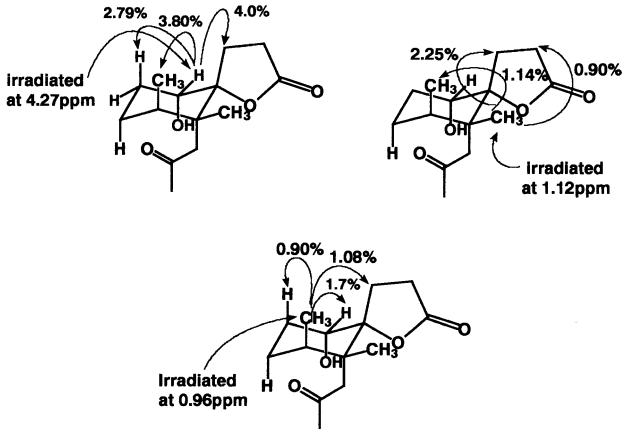


Figure 5. NOESY experiments with synthetic *epi*-pathylactone A.

NMR data were incorrectly assigned, particularly those for the carbinolic group.

3. Conclusion

In conclusion, this simple and direct approach has allowed us to construct the highly functionalized carbon skeleton of a rare type of nor-sesquiterpene from marine origin, in nine steps from 2-methylcyclohexenone, with an overall yield of 10%. Our results suggest that the spectral data proposed for natural pathylactone needs to be revised.

The above synthesis exemplifies a flexible approach that can be applied to the preparation of a number of derivatives of this class of sesquiterpenes.

Additional modifications to this strategy are ongoing in our laboratory, aiming at the total synthesis of (±)-napalilactone (**2**) and other non-natural spirolactone nor-sesquiterpenes.

4. Experimental

4.1. General

The ^{1}H and ^{13}C NMR spectra were recorded on a Varian Gemini BB-300 at 300 and 75.4 MHz, respectively. ^{1}H and ^{13}C NMR spectra were also recorded on an Inova 500 and 100 MHz, respectively. The mass spectra were recorded using a HP model 5988 A CG/MS or an Autospec–Micromass–EBE–high resolution equipment. The melting points were measured in open capillary tubes using an electrothermal apparatus, model 9100, and are uncorrected. Purifications and separations by column chromatography were performed on silica gel, using normal or flash chromatography. Ether and THF were distilled from benzophenone ketyl under nitrogen. Dichloromethane was distilled from CaH_2. TLC visualization was achieved by spraying with 5% ethanolic phosphomolybdic acid and heating. All the organolithium reagents were purchased from Aldrich Chemical Co.

4.1.1. (±)-2-Allyl-2,3-dimethylcyclohexan-1-one (6a/b). To a suspension of CuI (7.79 g, 41.0 mmol) in anhydrous ether (90 mL) was added an ethereal solution of methyllithium (65 mL, 82.0 mmol, ca. 1.25 mol dm^3), at 0°C, under N_2 atmosphere. After 15 min at 0°C, a solution of **7** (3.0 g, 27.27 mmol) in anhydrous ether (30 mL) was added to the ethereal solution of lithium dimethylcuprate. After 60 min at 0°C, the solvent was removed under reduced pressure. (*Caution: Avoid drying the reaction media completely as it is well known in the literature[14] that some dry RCu compounds can explode.*) To the resulting wet yellow solid was added DME (65 mL) under a N_2 atmosphere, giving rise to a greenish black solution, to which allyl bromide (19.0 mL, 218 mmol) was added, at 0°C. The final solution was stirred for 15 min. After that, the reaction was quenched with a saturated solution of $NaHCO_3$ (200 mL), followed by the addition of a 10% solution of NH_4OH (45 mL). The blue aqueous phase was extracted with pentane (3×200 mL). The combined organic layers were washed with a 10% solution of NH_4OH (50 mL) and distilled water (100 mL). The organic phase was dried over anhydrous $MgSO_4$ and the solvent was removed under reduced pressure. The oily residue was purified by flash column chromatography (silica gel 230–400 mesh, hexane/ethyl acetate 50:1 v/v) to furnish ketone *cis*-**6a** (0.68 g, 15%) and ketone *trans*-**6b** (2.74 g, 62%), as colorless oils. Ketone *cis*-**6a**: IR (ν_{max}, cm^{-1}, film) 3073, 2964, 2938, 2871, 2353, 1708 (CO), 1641, 1458, 1386, 1319, 1141, 1034, 939, 909, 808; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.61–5.54 (m, 1H), 5.07–5.0 (m, 2H), 2.49 (dd, J=14.0 and 7.6 Hz, 1H), 2.42–2.38 (m, 1H), 2.34–2.30 (m, 1H), 2.11 (dd, J=14.0 and 7.0 Hz, 1H), 2.03–1.97 (m, 1H), 1.75–1.64 (m, 4H), 1.09 (s, 3H), 0.98 (d, J=6.6 Hz, 3H); Ketone *trans*-**6b**: IR (ν_{max}, cm^{-1}, film) 3073, 2960, 2924, 2871, 2353, 1706 (CO), 1634, 1456, 1385, 1319, 1141, 1034, 909, 808; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.80–5.66 (m, 1H), 5.07–5.0 (m, 2H), 2.52 (dd, J=14.0 and 8.4 Hz, 1H), 2.47–2.28 (m, 2H), 2.17 (dd, J=14.0 and 8.4 Hz), 2.0–1.87 (m, 2H), 1.85–1.75.4 (m, 1H), 1.74–1.65 (m, 1H), 1.64–1.50 (m, 1H), 1.0 (s, 3H), 0.91 (d, J=7.0 Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 216.2, 135.4, 117.6, 52.3, 40.8, 38.5, 38.4, 29.1, 24.3, 18.9, 15.2; MS (70 eV, *m/z*): 166 (M^+, 30%), 151 (100%), 133 (15%), 123 (45%), 109 (65%), 95 (62%), 70 (83%), 61 (92%); HRMS (M^+) Calcd for $C_{11}H_{18}O$ 166.13577; Found 166.13587.

4.1.2. 1-[(4-Methoxybenzyl)oxy)]-3-propyl iodide (10). To a suspension of NaH (1.6 g, 39.6 mmol, 60% in mineral oil, washed with dry hexane before use) in dry THF (220 mL), at 0°C, under argon, was added 1,3-propanediol (1.3 g, 33 mmol). The resulting mixture was warmed to room temperature and stirred for 1 h. After this time, the mixture was cooled to 0°C and, to the cooled suspension, was added tetrabutylammonium iodide (2.44 g, 6.61 mmol) and *p*-methoxybenzylchloride (PMBCl, 5.4 mL, 39.6 mmol). The reaction mixture was warmed again to room temperature and stirred for 24 h. The reaction mixture was subsequently hydrolysed by the addition of a saturated solution of NH_4Cl (100 mL) and extracted with ethyl ether (2×250 mL). The organic phase was washed with a saturated solution of NH_4Cl (75.4 mL), distilled water (2×75.4 mL), brine (2×75.4 mL) and dried over anhydrous Na_2SO_4. After evaporation of the solvent under reduced pressure, the residue was purified by column chromatography to furnish 1-[(4-methoxybenzyl)oxy)]-3-propanol (5.43 g, 84%), as a colorless oil. IR (ν_{max}, cm^{-1}, film): 3412, 3007, 2948, 2871, 2062, 1997, 1896, 1622, 1468, 1373, 1313, 1260, 1177, 1087, 1034, 832; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 (d, J=8.8 Hz, 2H), 6.87 (d, J=8.8 Hz, 2H), 4.44 (s, 2H), 3.79 (s, 3H), 3.75 (t, J=6.0 Hz, 2H), 3.62 (t, J=6.0 Hz), 2.65–2.25 (bs, 1H, exchangeable with D_2O), 1.84 (quint, J=6.0 Hz, 2H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 159.2, 130.1, 129.2, 113.8, 72.8, 68.9, 61.7, 55.2, 32.0.

To a solution of the alcohol obtained above (3.0 g, 13.3 mmol) in dry dichloromethane (105 mL) was slowly added, at 0°C, triethylamine (2.3 mL, 16.8 mmol) and mesyl chloride (1.55 mL, 20 mmol). To the resulting mixture was added a solution of 4-dimethylaminopyridine (DMAP) in dry dichloromethane (5 mL). The final solution was stirred for 2 h at room temperature, after which cold water

(100 mL) was added to the reaction and the mixture was extracted with ethyl acetate (2×100 mL). The combined organic layers were washed with HCl (0.1 mol dm^3, 50 mL), $NaHCO_3$ 5% (2×50 mL) and brine (50 mL). The organic layer was dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure. The residue (4.18 g, quantitative yield) was sufficiently pure (by TLC) to be used in the next step without purification.

To a solution of the mesylate (4.10 g, 15.0 mmol) in acetone (156 mL) was added sodium iodide (11.25 g, 75.4 mmol). The resulting mixture was refluxed, under argon, for 6 h. After cooling to room temperature, distilled water (260 mL) was added and the mixture was extracted with ethyl ether (2×200 mL). The combined organic layers were washed with brine (2×130 mL). The aqueous phases were combined and extracted with more ethyl ether (2×200 mL). The organic layers were combined and dried over anhydrous Na_2SO_4. After evaporation of the solvent, the residue was purified by column chromatography to furnish iodide **11** (4.5 g, 98%). IR (ν_{max}, cm^{-1}, film) 3001, 2936, 2894, 2865, 1616, 1581, 1521, 1462, 1373, 1307, 1248, 1177, 1093, 1034, 826; ^1H NMR (300 MHz, $CDCl_3$) δ 7.26 (d, J=8.8 Hz), 6.88 (d, J=8.8 Hz, 2H), 4.44 (s, 2H), 3.80 (s, 3H), 3.51 (t, J=6.0 Hz, 2H), 3.29 (t, J=6.7 Hz, 2H), 2.07 (quint, J=6.0 Hz, 2H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 159.2, 130.3, 129.3, 113.8, 72.7, 69.3, 55.2, 33.5, 3.5.

4.1.3. (±)-2-Allyl-1-[3-(4-methoxybenzyloxy)propyl]-2,3-dimethylcyclohexan-1-ol (11a/b). To a stirred solution of the iodide **10** (0.91 g, 3.0 mmol) in anhydrous ether (20 mL) was added *t*-butyllithium (4.48 mL, 3.0 mmol) at −23°C, under a N_2 atmosphere. The resulting solution was stirred for 20 min at −23°C and allowed to warm to 0°C, before a solution of the ketone **6b** (0.33 g, 2.0 mmol) in anhydrous ether (20 mL) was slowly added (via canula). The final solution was stirred for 60 min at 0°C. The reaction medium was quenched with a saturated solution of NH_4Cl (13 mL) and extracted with ether (2×65 mL). The combined organic layers were washed with a saturated solution of NH_4Cl (40 mL), distilled water (2×40 mL) and finally brine (2×40 mL). The combined aqueous layers were extracted twice with ether (65 mL). The combined organic layers were dried over $MgSO_4$, and the solvent was removed under reduced pressure. The mixture of diastereoisomeric alcohols (50:50 ratio by CG) was easily separated by flash column chromatography (silica gel 230–400 mesh, hexane/ethyl acetate 99:1 and 95:5 v/v) to furnish the alcohol **11a** (0.24 g, 46% based on the recovered starting material) and the alcohol **11b** (0.24 g, 46% based on the recovered starting material). Alcohol **11a**: IR (ν_{max}, cm^{-1}, film) 3459, 3079, 2936, 2871, 1616, 1515, 1474, 1373, 1313, 1248, 1183, 1099, 1046, 915, 826, 749; ^1H NMR (300 MHz, $CDCl_3$) δ 7.26 (d, J=8.8 Hz, 2H), 6.88 (d, J=8.8 Hz, 2H), 6.10 (m, 1H), 5,.07 (m, 1H), 5.02 (m, 1H), 4.44 (s, 2H), 3.80 (s, 3H), 3.49–3.45 (m, 2H), 2.24–2.11 (m, 2H), 2.0–1.92 (m, 1H), 1.81–1.67 (m, 2H), 1.64–1.43 (m, 2H), 1.39–1.21 (m, 2H), 1.0 (s, 3H), 0.84 (d, J=6.6 Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 159.1, 138.3, 130.7, 129.1, 116.5, 113.7, 77.3, 72.3, 70.7, 55.2, 45.1, 41.5, 37.5, 30.8, 30.3, 30.1, 23.3, 22.0, 16.6, 13.0; MS (70 eV, *m*/*z*): 346 (M^+, 3%), 287 (2%), 207 (6%), 121 (100%), 77 (7%); HRMS (M^+) Calcd for $C_{22}H_{34}O_3$ 346.25080; Found: 346.25072; Alcohol **11b**: IR (ν_{max}, cm^{-1}, film): 3459, 3079, 2954, 2936, 2859, 1616, 1527, 1468, 1367, 1307, 1248, 1183, 1111, 1046, 927, 826; ^1H NMR (300 MHz, $CDCl_3$) δ 7.26 (d, J=8.8 Hz, 2H), 6.87 (d, J=8.8 Hz, 2H), 6.14 (m, 1H), 5.08 (m, 1H), 5.01 (m, 1H), 4.43 (s, 2H), 3.80 (s, 3H), 3.50–3.40 (m, 2H), 2.37 (dd, J=10.0 and 9.5 Hz, 1H), 2.25–2.13 (m, 2H), 1.95 (sl, exchangeable with D_2O, 1H), 1.79–1.22 (m, 10H), 0.85 (d, J=6.6 Hz, 3H), 0.78 (s, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 159.0, 138.8, 130.6, 129.2, 116.2, 113.7, 77.4, 72.3, 70.8, 55.2, 44.7, 39.9, 33.3, 31.8, 31.5, 30.2, 23.4, 21.1, 17.3, 16.1; MS (70 eV, *m*/*z*): 346 (M^+, 3%), 287 (2%), 207 (6%), 121 (100%), 77 (7%); HRMS (M^+) Calcd for $C_{22}H_{34}O_3$ 346.25080; Found: 346.25072.

4.1.4. (±)-6-Allyl-1-[3-(4-methoxybenzyloxy)propyl]-5,6-dimethylcyclohex-1-ene (5). To a stirred solution of the diastereoisomeric alcohols **11a/b** (0.34 g, 1.0 mmol) in dry pyridine (6 mL) was added 1,8-diazabicyclo[4.3.0]undec-7-ene (DBU, 0.28 mL, 3.0 mmol) and phosphorus oxychloride ($POCl_3$, 0.45 mL, 3.0 mmol), at 0°C. The resulting mixture was stirred at room temperature for 24 h, after which the reaction was cooled to 0°C and acetyl acetate (30 mL) and cold water (30 mL) were then carefully added. The organic phase was separated, washed successively with water (1×20 mL), and brine (1×20 mL) and dried over $MgSO_4$. After evaporation of the solvent, the residue was purified by column chromatography to furnish alkene **5** (0.25 g, 78%), contaminated with a small amount of the exo alkene (≤5%, as determined by GC on a HP column). Alkene **5** was used in the next step without purification. IR (ν_{max}, cm^{-1}, film) 3079, 2966, 2924, 2853, 1616, 1521, 1474, 1248, 1093, 1040, 820; ^1H NMR (300 MHz, $CDCl_3$) δ 7.26 (d, J=8.8 Hz, 2H), 6.87 (d, J=8.8 Hz, 2H), 5.67–5.53 (m, 1H), 5.43 (bs, 1H), 5.03–4.94 (m, 2H), 4.43 (s, 2H), 3.79 (s, 3H), 3.46 (t, J=6.6 Hz, 2H), 2.32–2.24 (m, 1H), 2.12 (dd, J=14.8 and 8.4 Hz, 1H), 2.05–1.92 (m, 4H), 1.79–1.63 (m, 3H), 1.53–1.31 (m, 2H), 0.87 (s, 3H), 0.84 (d, J=7 Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 159.0, 142.1, 135.9, 130.7, 129.2, 121.8, 116.2, 113.7, 72.4, 70.1, 55.2, 41.4, 40.7, 33.9, 28.8, 26.9, 26.5, 24.9, 20.8, 15.7; MS (70 eV, *m*/*z*): 328 (M^+, 2%), 287 (2%), 207 (6%), 121 (100%), 77 (7%); HRMS (M^+) Calcd for $C_{22}H_{32}O_2$ 328.24043; Found: 328.25042.

4.1.5. (±)-2-Allyl-1-[(3-methoxybenzyloxy)propyl)]-2,3-dimethyl-7-oxabicyclo[4.1.0]heptane (4). To a stirred solution of alkene **5** (0.3 g, 0.91 mmol) in dichloromethane (15 mL) was added *m*-chloroperbenzoic acid (MCPBA, 77%; 0.225 g, 1.0 mmol) at 0°C. The reaction mixture was then stirred at 0°C for 8 h, after which, a 2 mol^{-1} solution of potassium hydroxide (3.0 mL) was added and the organic phase separated. The aqueous phase was re-extracted with dichloromethane (3×10 mL). The combined organic layers were dried over $MgSO_4$, and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane, 2:98) to furnish the epoxides **4a** and **b**, as a mixture of diastereoisomers (0.276 g, 88%). IR (ν_{max}, cm^{-1}, film) 3073, 2954, 2936, 2853, 1640, 1616, 1587, 1509; ^1H NMR (300 MHz, $CDCl_3$) δ 7.24 (d, J=8.8 Hz, 2H), 6.87 (d, J=8.8 Hz, 2H), 6.04–5.90 (m, 1H), 5.84–5.71 (m, 1H), 5.09–4.98 (m, 2H), 4.41 (s, 2H), 3.79 (s, 3H), 3.58 (dd, J=13.4 and 7.0 Hz, 1H), 3.48–3.34 (m, 2H), 3.08 (bs, 1H), 2.40–2.12 (m, 3H), 2.04–

1.08 (m, 10H), 0.89 (s, 3H), 0.76 (d, J=6.0 Hz, 3H), 0.74 (d, J=6.0 Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 159.0, 134.0, 131.0, 129.5, 121.8, 117.5, 114.0, 72.2, 71.5, 64.0, 59.0, 42.0, 40.0, 39.5, 34.5, 29.5, 28.5, 27.5, 24.5, 24.0, 22.0, 18.5, 17.5; MS (70 eV, m/z): 344 (M^+, 2%), 303 (2%), 223 (2%), 167 (12%), 138 (17%), 121 (100%); HRMS (M^+) Calcd for $C_{22}H_{32}O_2$ 344.23515; Found: 344.23548.

4.1.6. (±)-10-Allyl-9,10-dimethyl-1-oxaspiro[4.5]decan-6-ol (3a/b). To a stirred solution of epoxyether **4a/b** (276 mg, 0.8 mmol) in a mixture of CH_2Cl_2 (20 mL) and H_2O (1.11 mL) was added DDQ (0.274 g, 1.2 mmol). The reaction medium was stirred at room temperature for 2.5 h. The reaction mixture was then diluted by addition of a saturated solution of $NaHCO_3$ (20 mL) and the aqueous phase was extracted with ethyl ether (3×50 mL). The organic layer was separated and washed successively with a saturated solution of $NaHCO_3$, and then NaCl and dried over $MgSO_4$. After evaporation under reduced pressure, the residue was purified by silica gel (230–400 mesh) column chromatography (hexane/ethyl acetate 95:5) to provide ethers **3a** and **b** (0.088 and 0.070 g, respectively, 88% yield), as colorless oils. Spiroether **3a**: IR (ν_{max}, cm^{-1}, film): 3446, 3072, 2941, 2879, 1634, 1459, 1391, 1067, 1036, 911; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.99–5.85 (m, 1H), 5.01–4.97 (m, 1H), 4.95–4.94 (m, 1H), 3.86–3.79 (m, 2H), 3.75 (t, J=7.5 Hz, 1H), 2.35 (dd, J=14.6, 7.3 Hz, 1H), 2.24 (dd, J=14.6 and 7.3 Hz, 1H), 2.10–1.79 (m, 6H), 1.65–1.36 (m, 3H), 0.93 (s, 3H), 0.89 (d, 3H, J=7.3 Hz); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 137.1, 115.6, 90.2, 72.4, 68.4, 43.9, 40.7, 34.4, 28.0, 27.9, 27.0, 25.6, 18.4, 15.8; MS (70 eV, m/z): 224 (M^+, 30%), 183 (10%), 165 (30%), 113 (100%), 97 (20%), 71 (32%), 55 (56%); HRMS (EI): m/z Calcd for $C_{14}H_{24}O_2$ $[M]^+$ 224.17763, Found 224.17721; Calcd for $C_{14}H_{24}O_2$ 74.95; H 10.78%, Found C 74.91; H 10.74%. Spiroether **3b**: IR (ν_{max}, cm^{-1}, film): 3442, 3073, 2972, 2938, 2878, 1635, 1467, 1386, 1064, 909; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.05–5.91 (m, 1H), 5.0–4.9 (m, 2H), 3.98–3.91 (m, 2H), 3.87 (t, 1H, J=7 Hz), 2.19 (dd, J=15.0 and 7.3 Hz, 1H), 2.06 (dd, J=15.0 and 7.3 Hz, 1H), 2.0–1.78 (m, 5H), 1.53–1.27 (m, 4H), 0.90 (s, 3H), 0.85 (d, 3H, J=6.6 Hz). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 137.4, 114.6, 92.3, 76.6, 69.8, 44.6, 41.1, 37.5, 30.5, 28.7, 27.1, 24.9, 15.9, 13.9; MS (70 eV, m/z): 224 (M^+, 55%), 209 (5%), 183 (8%), 165 (96%), 153 (10%), 113 (100%), 97 (30%), 85 (25%), 71 (53%), 55 (45%); HRMS (EI): m/z Calcd for $C_{14}H_{24}O_2$ $[M]^+$ 224.17763; Found 224.17790. Calcd for $C_{14}H_{24}O_2$ 74.95%, H 10.78%; Found C 74.94%, H 10.77%.

4.1.7. (±)-6-*tert*-Butyldimethylsilyloxy-10-allyl-9,10-dimethyl-1-oxaspiro[4.5]-decan-6 (12). To a stirred solution of spiroether **3a** (0.11 g, 0.49 mmol) in dichloromethane was added triethylamine (275.4 μL, 2.0 mmol) at 0°C. The resulting solution was stirred for 5 min, after which *t*-butyldimethylsilane triflate (TBSOTf, 226 μL, 0.98 mmol) was added and the reaction mixture was allowed to warm to room temperature and then stirred for 1 h. After that, the reaction mixture was quenched with a saturated solution of ammonium chloride (14 mL) and extracted with dichloromethane (3×20 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate 95:5) to give **12** (0.153 g, 92%), as a colorless oil. IR (ν_{max}, cm^{-1}, film): 3071, 2957, 2930, 2887, 1637, 1484, 1382, 1257, 1062, 910, 839, 785; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.10–5.96 (m, 1H), 4.96–4.88 (m, 2H), 3.85–3.66 (m, 2H), 3.55 (m, 1H), 2.26 (m, 1H), 2.17–1.26 (m, 10H), 2.0–1.78 (m, 5H), 0.93 (s, 3H), 0.91 (s, 9H), 0.84 (d, J=6.9 Hz, 3H); 0.06 (s, 6H). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 138.1, 114, 89.7, 72.8, 67.9, 43.5, 41.7, 34.7, 29.4, 26, 25.9, 25.6, 18.1, 17.6, 16.3, −4.1; MS (70 eV, m/z): 338 (M^+, 90%), 281 (90%), 239 (26%), 165 (80%), 115 (100%), 75 (92%); HRMS (EI): m/z Calcd for $C_{20}H_{38}O_2Si$ $[M]^+$ 338.26411; Found 338.26416.

4.1.8. 1-[(±)-10-*t*-Butyldimethylsilyloxy-6,7-dimethyl-1-oxaspiro[4.5]dec-1-yl]acetone (13). To a stirred solution of silyl spiroether **12** (0.131 g, 0.19 mmol) in *N*,*N*-dimethylacetamide (0.58 mL) were added $PdCl_2$ (0.034 g, 0.19 mmol), $Cu(OAc)_2{\cdot}H_2O$ (0.078 g, 0.39 mmol) and water (0.083 mL). The resulting suspension was stirred at room temperature, under an enriched oxygen atmosphere, for 3 days. The reaction mixture was then quenched with a 3 mol^{-1} solution of hydrogen chloride (0.5 mL) and extracted with ethyl ether (5×20 mL). The combined organic layers were washed successively with a solution of $NaHCO_3$ (2×25 mL) and brine (2×30 mL), dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane 20:80) to furnished methyl ketone **13** (0.077 g, 56%), as a colorless oil. IR (ν_{max}, cm^{-1}, film): 2956, 2932, 2886, 2857, 1709, 1470, 1366, 1256, 1134, 1058, 942, 838; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.74–3.67 (m, 1H), 3.61–3.53 (m, 2H), 2.41–2.24 (m, 3H), 2.12 (s, 2H), 2.05–1.78 (m, 5H), 1.66–1.26 (m, 3H), 0.98 (s, 3H), 0.89 (s, 9H), 0.88 (d, J=6.6 Hz, 3H), 0.05 (s, 6H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 207.5, 89.23, 70.9, 66.8, 49.8, 46.9, 34.2, 31.9, 29.1, 28.0, 25.9, 25.6, 24.5(×2), 18.6, 16.9, −4.2, −5.1; MS (70 eV, m/z): 354 (M^+, 17%), 297 (50%), 239 (100%), 198 (25%), 153 (45%), 111 (85), 75 (90%); Calcd for $C_{20}H_{38}O_3Si$ $[M]^+$ 354.25902; Found 354.25907.

4.1.9. (±)-10-Hydroxy-6,7-dimethyl-6-(2-oxopropyl)-1-oxaspiro[4,5]decan-2-one (1). To a stirred solution of silyl methylketone **13** (0.057 g, 0.16 mmol) in ethyl acetate (0.6 mL) were added $RuCl_3{\cdot}H_2O$ (0.007 g, 0.032 mmol) and a 10% aqueous solution of $NaIO_4$ (1.71 mL, 0.8 mmol). The suspension was stirred at room temperature for 23 h, after which, the reaction mixture was quenched with a saturated solution of $Na_2S_2O_3$ and extracted with ethyl acetate (3×20 mL). The combined organic layers were dried over Na_2SO_4, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate 90:10) to furnish a spirolactone **14** (0.0495 g, 88%), as an oil. IR (ν_{max}, cm^{-1}, film): 2955, 2931, 2883, 2859, 1777, 1705, 1471, 1259, 1255, 1189, 1057, 1020, 840, 780; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.94 (dd, J=10.0 and 5.0 Hz, 1H), 2.73 (d, J=14.0 Hz, 1H), 2.58 (d, J=14.0 Hz, 1H), 2.52–2.15 (m, 4H), 2.17 (s, 3H), 1.81–1.46 (m, 5H), 1.09 (s, 3H), 0.97 (d, J=7.3 Hz, 3H), 0.88 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.5, 176.4, 92.3, 72.2, 48.1, 45.4, 34.1, 32.9, 29.1, 28.1, 25.8, 25.7, 23.7, 17.9, 17.1,

16.2, −4.4, −5.0; MS (70 eV, *m/z*): 368 (M^+, 10%), 311 (20%), 253 (100%), 171 (13%), 119 (17%), 75 (43%), 74 (38%); HRMS (EI): *m/z* Calcd for $C_{20}H_{36}O_4Si$ 368.23829; Found 368.23823; Calcd for $C_{20}H_{36}O_4Si$ C 65.17, H 9.84%; Found C 65.12, H 9.81%.

A stirred solution of silyl spirolactone **14**, prepared as described earlier (0.041 g, 0.11 mmol) in a mixture of acetonitrile/hydrogen fluoride (CH_3CN:HF, 1:1; 2 mL, 48% w/v of HF in water), was stirred, at room temperature, for 2 h. After that, the reaction mixture was diluted with distilled water (3 mL) and a saturated solution of $NaHCO_3$ (2 mL). Then, the aqueous phase was extracted with dichloromethane (2×10 mL). The combined organic phases were dried over Na_2SO_4 and evaporated under reduced pressure. The residue was purified by silica gel (70–230 mesh) column chromatography (hexane/ethyl acetate 70:30) to provide **1** (0.026 g, 90%) as a viscous oil, which slowly crystallizes on standing. Mp 43–45°C (recrystallized from cold hexane); IR (ν_{max}, cm^{-1}, film): 3460, 2932, 2886, 1778 (O–C═O), 1709 (C═O), 1470, 1360, 1256, 1232, 1198, 1006; ^1H NMR (500 MHz, $CDCl_3$) δ 3.99 (dd, J=10.9 and 4.27 Hz, 1H), 2.77 (d, J=15.5 Hz, 1H), 2.67 (d, J=15.5 Hz, 1H), 2.71–2.64 (m, 1H), 2.58–2.46 (m, 1H), 2.41–2.33 (m, 2H), 2.29 (bs, 1H), 2.26–2.21 (m, 1H), 2.17 (s, 3H), 1.90–1.84 (m, 1H), 1.78–1.73 (m, 1H), 1.68–1.60 (m, 1H), 1.50–1.44 (m, 1H), 1.14 (s, 3H), 0.98 (d, J=7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.7, 177.3, 93.1, 71.1, 47.6, 45.1, 33.7, 32.9, 29.4, 27.0, 25.7, 23.4, 17.2, 15.9; MS (70 eV, *m/z*): 254 (5%), 236 (12%), 221 (3%), 197 (30%), 179 (77%), 167 (85%), 152 (50%), 149 (55%), 125 (30%), 115 (25%), 111 (13%), 85 (23%), 71 (20%), 57 (35%); HRMS (EI): *m/z* Calcd for $C_{14}H_{22}O_4$ 254.151809; Found 254.151805; Calcd for $C_{14}H_{22}O_4$ C 66.12, H 8.72%; Found C 66.10, H 8.70%.

4.1.10. (±)-6-Allyl-10-*t*-butyldimethylsilyloxy-6,7-dimethyl-1-oxaspiro[4.5]decane (15). This compound was prepared using the same experimental protocol described earlier for compound **13**, using spiroether **3b** (0.05 g, 0.223 mmol) as starting material. Chromatographic purification (hexane/ethyl acetate 90:10) furnished 0.071 g (94%) of **15**, as a colorless oil. IR (ν_{max}, cm^{-1}, film): 3072, 2954, 2929, 2885, 2860, 1634, 1466, 1248, 1092, 837, 675; ^1H NMR (500 MHz, $CDCl_3$) δ 6.03–5.94 (m, 1H), 4.96–4.88 (m, 2H), 3.86–3.82 (m, 3H), 2.24–2.21 (m, 1H), 2.08–2.03 (m, 2H), 1.92–1.86 (m, 1H), 1.84–1.69 (m, 3H), 1.50–1.26 (m, 4H), 0.9 (s, 3H), 0.88 (m, 9H), 0.85 (d, J=6.6 Hz, 3H), 0.06 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.8, 114.2, 91.4, 74.0, 69.0, 44.7, 41.3, 37.6, 29.5, 28.7, 26.9, 25.9, 25.7, 18.0, 16.1, 14.1, −4.6; MS (70 eV, *m/z*): 338 (M^+, 24%), 281 (90%), 239 (30%), 211 (5%), 190 (40%), 165 (85%), 147 (70%), 75 (100%); HRMS (EI): *m/z* Calcd for $C_{14}H_{38}O_2Si$ 338.26411; Found 338.26415.

4.1.11. 1-[(±)-10-Ethoxy-6,7-dimethyl-1-oxaspiro[4.5]-dec-6-yl]acetone (16). This compound was prepared following the same experimental protocol described earlier for compound **13**, using the silyl spiroether **15** (0.061 g, 0.18 mmol) as starting material. Chromatographic purification (hexane/ethyl acetate 80:20) gave methylketone **16** (0.032 g, 50%) as a colorless oil. IR (ν_{max}, cm^{-1}, film): 2955, 2931, 2889, 2859, 1707, 1459, 1357, 1255, 1093, 1081, 840; ^1H NMR (300 MHz, $CDCl_3$) δ 3.86–3.79 (m, 2H), 3.63–3.56 (m, 1H), 2.5–2.25 (m, 2H), 2.18 (s, 3H), 2.13–1.6 (m, 5H), 1.39–1.26 (m, 4H), 1.19 (s, 3H), 0.88 (s, 9H), 0.82 (d, J=6.6 Hz, 3H), 0.06 (s, 6H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 208.7, 91.3, 74.2, 69.0, 52.8, 47.5, 38.4, 31.6, 29.8, 28.2, 26.6, 26.0, 25.3, 18.1, 16.1, 15.7, −4.4; MS (70 eV, *m/z*): 354 (M^+, 20%), 297 (50%), 239 (95%), 198 (18%), 111 (80%), 75 (95%), 74 (100%); HRMS (EI): *m/z* Calcd for $C_{14}H_{38}O_3Si$ 354.25902; Found 354.25899.

4.1.12. (±)-3′,5′,6′-Trimethyl-3,4-dihydro-5*H*-spiro-[furan-2,9′-[2]oxabicyclo[3.3.1]non[3]en]-5-one (18). To a stirred solution of **16** (0.03 g, 0.08 mmol) in ethyl acetate (0.3 mL) was added $RuCl_3{\cdot}H_2O$ (0.004 g, 0.016 mmol) and a 10% aqueous solution of $NaIO_4$ (0.9 mL, 0.4 mmol). The suspension was stirred at room temperature for 23 h, after which, the reaction mixture was quenched with a saturated solution of $Na_2S_2O_3$ and extracted with ethyl acetate (3×10 mL). The combined organic phases were dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate 90:10) to furnish **17** (0.026 g, 84%), as an oil. IR (ν_{max}, cm^{-1}, film): 2953, 2927, 2856, 2859, 1776, 1700, 1466, 1259, 1221, 1098, 1014, 839, 781, 671; ^1H NMR (500 MHz, $CDCl_3$) δ 3.82–3.78 (m, 1H), 2.73 (d, J=14.0 Hz, 1H), 2.58 (d, J=14.0 Hz, 1H), 2.52–2.15 (m, 4H), 2.17 (s, 3H), 1.81–1.46 (m, 5H), 1.09 (s, 3H), 0.97 (d, J=7.3 Hz, 3H), 0.88 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.8, 177.2, 93.0, 72.2, 53.5, 46.6, 37.5, 31.8, 31.3, 30.4, 27.8, 21.8, 17.9, 15.7, 15.3, −4.9; MS (70 eV, *m/z*): 368 (M^+, 5%), 311 (90%), 253 (100%), 185 (40%), 123 (90%), 75 (95%); HRMS (EI): *m/z* Calcd for $C_{14}H_{22}O_4$ 368.23829; Found 368.23807.

A solution of silyl spirolactone **17** (0.020 g, 0.05 mmol) in a mixture of acetonitrile/hydrogen fluoride (CH_3CN:HF, 1:1; 1 mL, 48% w/v of HF in water) was stirred, at room temperature, for 2 h. After that, the reaction mixture was diluted with distilled water (3 mL) and a saturated solution of $NaHCO_3$ (2 mL). Then, the aqueous phase was extracted with dichloromethane (2×10 mL). The combined organic phases were dried over Na_2SO_4 and evaporated under reduced pressure. The residue was purified by silica gel (70–230 mesh) column chromatography (hexane/ethyl acetate 70:30) to provide **18** (0.011 g, 90%) as a viscous oil. IR (ν_{max}, cm^{-1}, film): 2966, 2929, 2873, 1777, 1677, 1453, 1383, 1204, 1036, 818; ^1H NMR (300 MHz, $CDCl_3$) δ 4.1 (d, J=0.7 Hz, 1H), 3.89 (bs, 1H), 2.56–2.49 (m, 2H), 2.32–2.22 (m, 1H), 2.18–1.96 (m, 2H), 1.75 (d, J=0.7 Hz, 3H), 1.66–1.46 (m, 2H), 1.35–1.21 (m, 2H), 1.13 (d, J=7.3 Hz, 3H), 0.98 (s, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 176.6, 150.6, 103.5, 86.3, 76.3, 40.0, 39.0, 28.2, 27.7, 25.0, 24.9, 19.3, 18.8, 16.3; Calcd for $C_{14}H_{20}O_3$ C 71.16, H 8.53%; Found C 71.12, H 8.50%.

4.1.13. (±)-*epi*-Pathylactone A (20). To a stirred solution of **1** (5 mg, 0.0196 mmol), at 0°C, in dry dichloromethane (1.5 ml) was added PPh_3 (1 mg, 0.039 mmol), diethyl azodicarboxylate (DEAD, 6 mg, 6 μL, 0.039 mmol) and acetic acid (2 mg, 2.5 μL, 0.039 mmol). The resulting solution was stirred at room temperature for 6 h, after which the

reaction mixture was diluted with dichloromethane (10 mL). The organic phase was washed with brine (2×5 mL), dried over Na_2SO_4 and was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate 90:10) to furnish **19** (3.6 mg, 62%), as a viscous yellow tinged oil. IR (ν_{max}, cm^{-1}, film): 2953, 2927, 1776, 1721, 1710, 1238, 1014; ^1H NMR (500 MHz, $CDCl_3$) δ 4.72 (dd, J=10.1 and 3.9 Hz, 1H), 2.73 (d, J=14.0 Hz, 1H), 2.58 (d, J=14.0 Hz, 1H), 2.52–2.15 (m, 4H), 2.2 (s, 3H), 2.17 (s, 3H), 1.81–1.46 (m, 5H), 1.09 (s, 3H), 0.97 (d, J=7.3 Hz, 3H), 0.88 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.8, 177.2, 170.3, 98.0, 72.2, 53.5, 50.8, 46.6, 37.5, 31.8, 31.3, 30.4, 27.8, 21.8, 17.9, 15.7; MS (70 eV, *m/z*): 296 (M^+, 5%), 281 (23%), 254 (90%), 237 (70%), 43 (100%); HRMS (EI): *m/z* Calcd for $C_{16}H_{24}O_5$ 296.1623; Found 296.1620.

To a solution of acetate **19** (3.6 mg, 0.012 mmol) in a mixture of THF/water (3:1, 1.5 mL), at room temperature, was added lithium hydroxide (2 mg, 0.06 mmol). The resulting suspension was stirred for 8 h. After that, the reaction mixture was evaporated and dissolved in ethyl acetate (10 mL). The organic phase was washed with a 5% solution of HCl (1×5 mL), distilled water (3×15 mL) and brine (1×5 mL). The organic phase was dried over Na_2SO_4 and evaporated under reduced pressure. The residue was purified by silica gel (70–230 mesh) column chromatography (hexane/ethyl acetate 80:20) to provide **20** (2.2 mg, 72%) as an amorphous solid. Mp 44–47°C (recrystallized from cold hexane) IR (ν_{max}, cm^{-1}, film): 2966, 2929, 2873, 1777, 1707, 1453, 1383, 1204, 1036, 818; ^1H NMR (500 MHz, $CDCl_3$) δ 4.27 (m, 1H), 2.80–2.73 (two doublet, J= 15.1 Hz, 2H), 2.67–2.48 (m, 2H), −2.38 (m, 1H), 2.30 (m, 2H), 2.09 (s, 3H), 2.0–1.78, (m, 2H), 1.79–1.44 (m, 2H), 0.96 (d, J=7.7 Hz, 3H), 1.12 (s, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 207.0, 177.0, 92.0, 65.0, 47.0, 45.3, 33.7, 32.2, 29.0, 27.0, 26.0, 24.0, 17.2, 15.9; MS (70 eV, *m/z*): 254 (15%), 236 (12%), 221 (3%), 197 (30%), 179 (77%), 167 (85%), 152 (50%), 149 (55%), 125 (30%), 115 (25%), 111 (13%), 85 (23%), 71 (20%), 57 (35%); HRMS (EI): *m/z* Calcd for $C_{14}H_{22}O_4$ 254.151809; Found 254.151805.

The ^1H (500 MHz) and ^{13}C NMR (125 MHz) spectra of **1** is provided as Supplementary Material.

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