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Total Synthesis of Plakortone B

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Dedicated to the memory of Professor Xian Huang

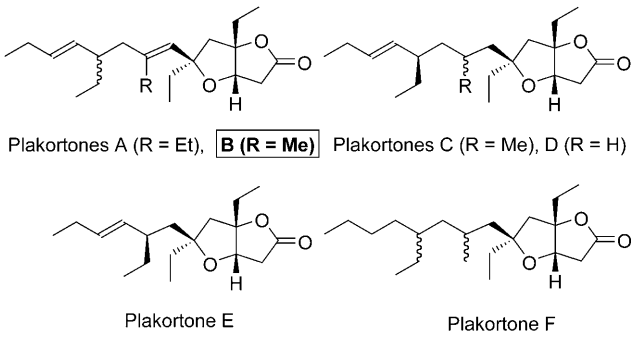
Abstract: Plakortone B is a naturally occurring bicyclic[3.3.0]furanolactone compound with attractive bioactivities. Although the relative configuration of plakortone B's central core had been established by NMR spectroscopic methods, the absolute configuration of its four stereocenters remained unknown. In the present paper, all four possible isomers of plakortone B were synthesized and one of these molecules was found to be identical with the natural plakortone B on the basis of ^{1}H, ^{13}C NMR spectra and specific rotation comparisons. Thus, the absolute configuration of the natural plakortone B was determined to be (3*S*,4*S*,6*R*,10*R*).

Keywords: asymmetric synthesis · chirality · natural products · plakortone B · structure elucidation

Introduction

Plakortones belong to a family of naturally occurring bicyclic[3.3.0]furanolactones isolated from the Caribbean sponges *Plakortis halichondrioides* (plakortones A–D)[1] and *Plakortis simplex* (plakortones B–F)[2]. These compounds are cardiac sacroplasmic reticulum Ca^{2+}-pumping ATPase activators that were found to be active at micromolar concentrations and relevant to the correction of cardiac muscle relaxation abnormalities.[1–3] They also exhibit in vitro cytotoxic activity on a murine fibrosarcoma cell line and represent a new family of lead compounds with potential pharmacological interest.[2] The structures of the plakortone family were established by NMR spectroscopic methods, and NOE difference data provided the relative configurations of their core structures. However, the absolute configurations of their stereocenters were not revealed in the initial structure elucidation.[1] Recently, the absolute configurations of plakortones B,[4d] D,[4a,b] and E[4c] were established by total syntheses, but the absolute configurations of the other three plakortones (A, C, and F) still remain unknown.

During our recent total synthesis of natural molecules starting from substituted furans, we have developed an enantioselective route towards functionalized bicyclic-[3.3.0]furanolactones,[5] and as a result, were aware that this key approach could also lead to plakortones. A program towards the total synthesis of plakortone B was therefore initiated in our laboratory. Due to the fact that the absolute configuration of plakortone B was still unknown at the time we began our synthetic work, our plan was to synthesize all four possible isomers (Scheme 1) to confirm the absolute configuration of the naturally occurring plakortone B by comparison of their spectral and physical data.



Since we were not aware of the absolute configuration of plakortone B when we first started, we achieved and reported an enantioselective route for the preparation of function-

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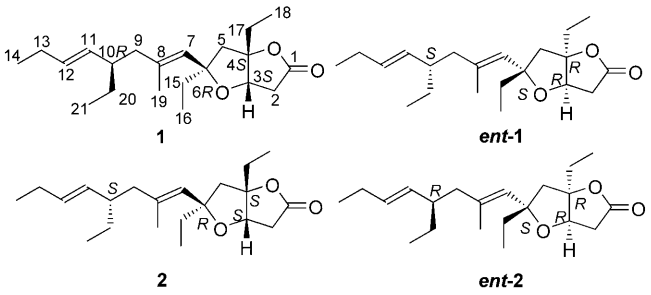
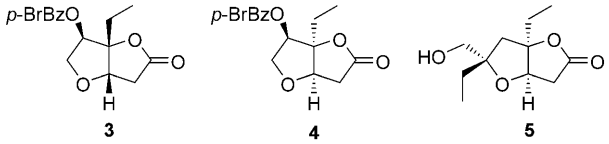


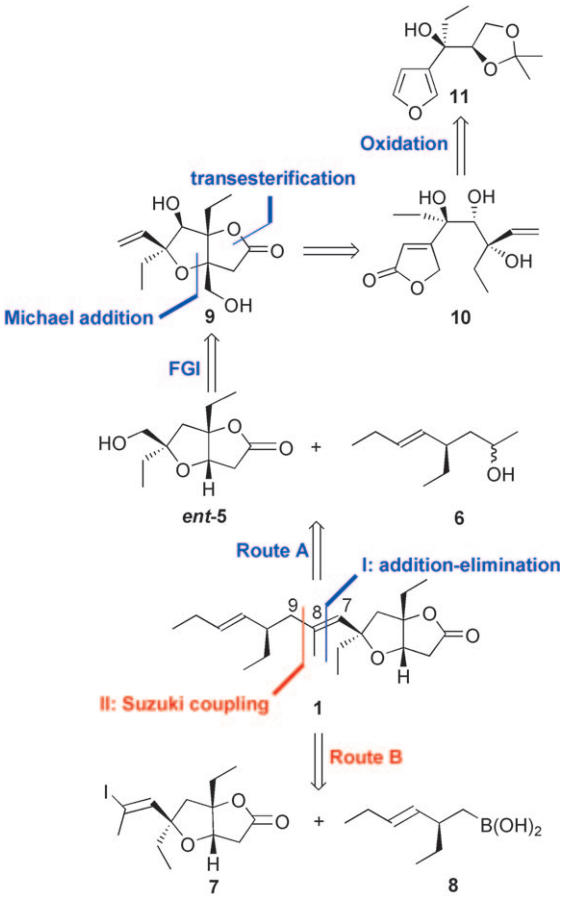
Scheme 1. All four possible absolute configurations of plakortone B.

alized bicyclic lactones **3**, **4**, and **5** in 2002.[6] In the same year, Kitching and Hayes reported an asymmetric total synthesis of plakortone D, the absolute configuration of which was assigned as (3*S*,4*S*,6*S*,10*R*).[4a] Based on the observations that plakortone B was also isolated from the same natural source[1,2] as well as on the total synthesis of plakortone B by Semmelhack and co-workers,[4d] the absolute configuration of plakortone B was also most likely to be (3*S*,4*S*,6*R*,10*R*) (Scheme 1, compound **1**). Therefore, compound **5**, which was previously prepared by us,[6a] might possess a central core that was an enantiomer of that of the natural plakortones. Herein, we report the total synthesis of plakortone B and the determination of its absolute configuration.



Results and Discussion

Because the natural plakortone B was most likely to have (3*S*,4*S*,6*R*,10*R*) absolute configuration, compound **1** was chosen as our first synthetic target. According to the convergent synthetic strategy, we envisioned that the target molecule could be achieved by coupling the corresponding central core and the side chain. Thus, two retrosynthetic disconnections were considered, generating *ent*-**5**[4a] and **6** (route A), and **7** and **8** (route B) as possible coupling components (Scheme 2). Route A was based on a disconnection



Scheme 2. Retrosynthetic analysis of compound **1**.

of the C7=C8 double bond and involved an addition–elimination strategy, which had been successfully applied in the total synthesis of plakortone D.[4a] Route B was based on a disconnection of the C8–C9 single bond and was expected to be realized by a Suzuki coupling reaction.[7] It should be noted at this point that only the approach based on route B gave pure compound **1** successfully, and that the approach based on route A only provided a mixture of compound **1** and its C7=C8 *Z* isomer.

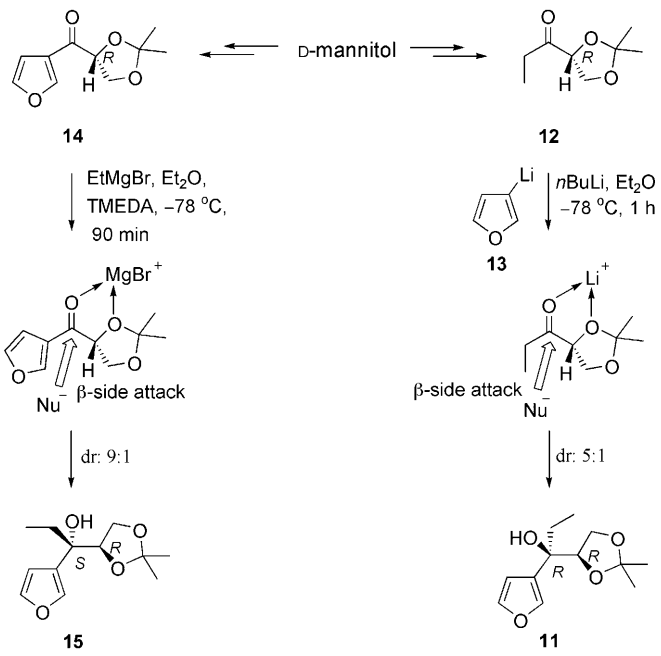
Retrosynthetic analysis of compound 1: As can be seen in Scheme 2, *ent*-**5**,[4a] **7** (the central core), **6**, and **8** (the side chain) would be the potential precursors after the corresponding disconnection of compound **1** (route A or B). The required *ent*-**5** is then derived from bicyclic lactone **9** by a series of functional group interconversions. For the preparation of **9**, we anticipated that the bicyclic[3.3.0] framework could be established from butenolide **10** through an intra-

Abstract in Chinese:

Plakortone B 是具有良好生理活性的雙環［3.3.0］四氫呋喃并內酯類天然產物。儘管 plakortone B 母核部分的相對構型已經通過核磁方法得以確定，但是其四個立體中心的絕對構型仍然未知。本文通過合成了 plakortone B 的所有四個可能異構體并比較它們的核磁數據和光學旋光值，其中一個異構體被確定与天然產物 plakortone B 相吻合，并確定了天然 plakortone B 的絕對構型為(3*S*, 4*S*, 6*R*, 10*R*)。

molecular Michael addition and a transesterification reaction.[5b] Butenolide **10** can, in turn, be derived from tertiary alcohol **11**, which has previously been prepared by us.[8] Iodide **7** can be obtained by a diastereoselective hydrostannylation reaction followed by an iodination reaction from the related alkyne, which was derived from the crucial precursor *ent*-**5**. The synthesis of side chains **6** and **8** was realized by a standard procedure (see the Supporting Information).[9]

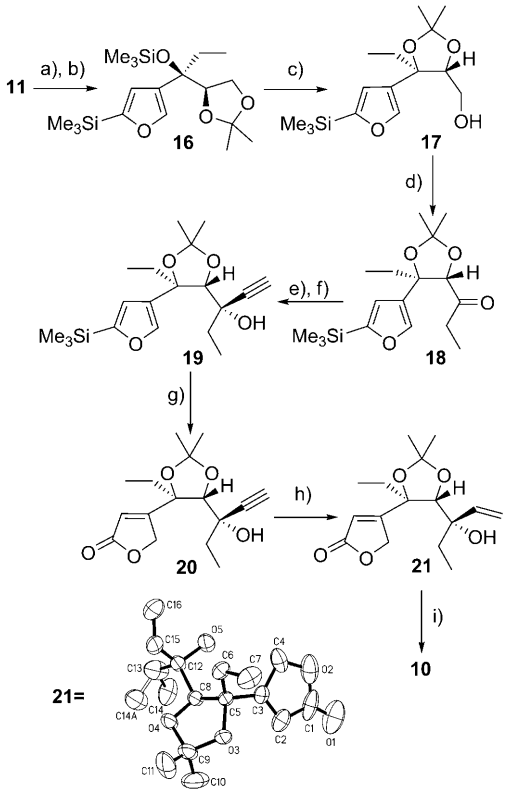
Construction of the central core *ent*-5: Our synthetic program for the preparation of the core *ent*-**5** required chiral alcohol **11** as a precursor. A highly diastereoselective preparation of alcohol **11** is depicted in Scheme 3.[8] Thus, when



Scheme 3. Preparation of optically pure starting materials **11** and **15**.

ketone **12**, which was prepared from D-mannitol, was treated with 3-lithiofuran (**13**), according to Cram's chelation control rule,[10] the nucleophile would preferentially attack from the less-hindered β-side, providing (2*R*,3*R*)-*syn*-alcohol **11** as the major product and (2*R*,3*S*)-*anti*-alcohol **15** as the minor product; the diastereoselectivity ratio was 5:1. In a similar manner, when ketone **14**, which was also derived from D-mannitol, was treated with a Grignard reagent (EtMgBr), (2*R*,3*S*)-*anti*-alcohol **15** was produced preferentially and the diastereoselectivity ratio was as high as 9:1. Compound **15** was previously employed by us to synthesize bicyclic lactone **5** in one of our programs.[6a] In this way, alcohols **11** and **15** were both derived from enantiopure (+)-2,3-*O*-isopropylidene-D-glyceraldehyde,[11] the absolute *R* configuration of our synthesized central cores could accordingly be established on the basis of this stereogenic center.

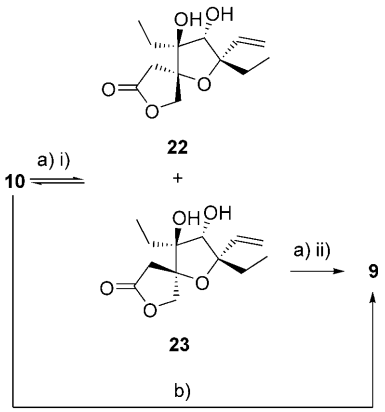
With the optically pure tertiary alcohol **11** in hand, we then started to synthesize the key intermediate butenolide **10** (Scheme 4). Protection of the tertiary alcohol **11**, followed by highly regiospecific silylation reaction, gave ether **16** in a high yield.[5b] After conversion of **16** into **17** by a general routine,[6a] the resulting primary alcohol **17** was converted into ketone **18** by a sequence of Swern oxidation,[12] EtMgBr addition, and PDC oxidation. Alcohol **19** was then prepared by a highly diastereoselective addition of trimethylsilylalkynyllithium to ketone **18**, followed by a regioselective desilylation. 2,4-Disubstituted furan **19** was converted into butenolide **20** by a peracetic acid oxidation established by Kuwajima and Urabe.[13] Butenolide **20** was partially hydrogenated over Lindlar's catalyst[14] to afford alkene **21**, which was deprotected to afford the required butenolide **10**. In addition, the absolute configuration of alkene **21** was established by X-ray crystallographic analysis.[33] With the aid



Scheme 4. Synthesis of butenolide **10**. a) Me_3SiCl, imidazole, 4-dimethylaminopyridine (DMAP), DMF, 0°C, 0.5 h, 95%; b) *n*BuLi (2.2 equiv), THF, −25°C, 0.5 h, then Me_3SiCl (1.05 equiv), −78°C, 0.5 h, 80%; c) i) 80% AcOH (aq.), 23°C, 24 h; ii) *t*$BuMe_2SiCl$, imidazole, DMAP, THF, 23°C, 0.5 h; iii) 2,2-dimethoxypropane, *p*-toluenesulfonic acid (cat.), THF, reflux, 5 h; iv) nBu_4NF (1.0 equiv), THF, 23°C, 3 h, 63% over 4 steps; d) i) $(COCl)_2$, DMSO, CH_2Cl_2, −78°C, 1 h, then Et_3N, −78→23°C, 0.5 h; ii) EtMgBr, THF, 0°C, 0.5 h; iii) pyridinium dichromate (PDC), 4 Å molecular sieves, CH_2Cl_2, 23°C, 24 h, 75% over 3 steps; e) Me_3SiCCH, *n*BuLi, THF, 0°C, 86%; f) nBu_4NF, THF, −10°C, 20 min, 90%; (g) CH_3CO_3H, NaOAc, CH_2Cl_2, 23°C, 24 h, 80%; h) Lindlar's catalyst, quinoline, H_2, MeOH, 23°C, 24 h, 95%; i) *p*-toluenesulfonic acid (20 equiv), MeCN, 23°C, 72 h, 80%.

of the known *R* configuration of **12**, the absolute configurations of the two new stereocenters formed in the previous reaction sequence were also confirmed.

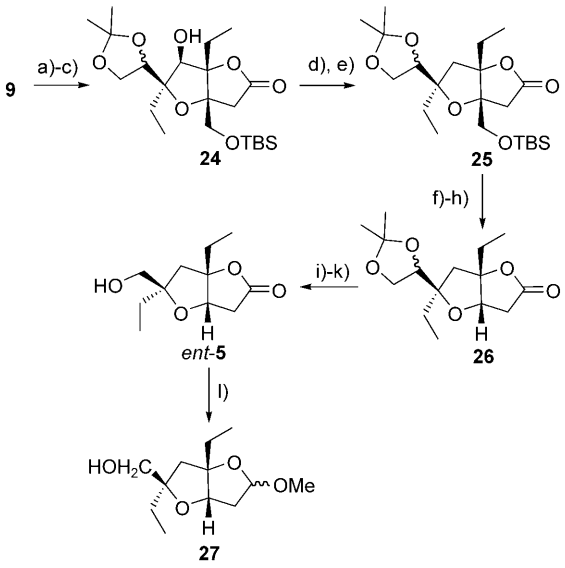
Butenolide **10** was converted into bicyclic lactone **9** by an intramolecular Michael addition followed by transesterification[5b] in 50% overall yield, together with the formation of the spirocyclic compound **22** in 28% yield (Scheme 5).



Scheme 5. Synthesis of bicyclic lactone **9**. a) i) Et_3N (100 equiv), toluene, reflux, 24 h; ii) 3N HCl (aq.), 23°C, 48 h, 50% for **9** and 28% for **22**; b) 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU) (0.1 equiv), toluene, reflux, 72 h, 90%.

Compound **22** was one of the two possible products (**22** and **23**) resulting from the intramolecular Michael addition reaction of **10**. Interestingly, we found that compound **22** could be completely transformed into **9** when DBU was used. It was assumed that butenolide **10** was obtained initially by a retro-Michael addition reaction of compound **22** when treated with DBU. Then **10** was transformed into the desired bicyclic lactone **9** through the same sequence as before. We presumed that the intramolecular Michael addition and the subsequent transesterification could be conducted in one pot by using DBU as a base. Further study showed that DBU could indeed readily promote this transformation, and bicyclic lactone **9** was obtained in 90% yield directly from butenolide **10** by using a catalytic amount of DBU in toluene upon heating to reflux for 72 h.

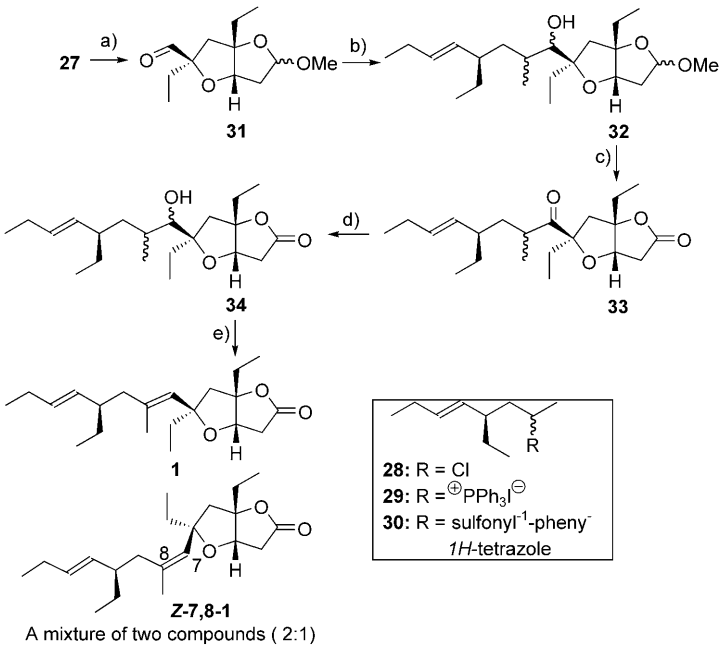
Bicyclic lactone **9** was transformed into the core *ent*-**5** by the sequence of reactions depicted in Scheme 6. After selective protection of the primary hydroxyl group of **9**, an osmium-catalyzed dihydroxylation[15] followed by protection with acetone, provided the desired secondary alcohol **24**. A Barton deoxygenation reaction[16] of **24** led to the formation of **25**. It is interesting to iterate that at this point in the synthetic sequence the secondary alcohol, with its *R* configuration originating from D-mannitol, had served its role in guiding the introduction of the other stereocenters, and was thus removed. Subsequently, desilylation, Dess–Martin periodinane oxidation,[17] and a reductive decarbonylation with Wilkinson's reagent,[18]converted **25** into **26**. After deprotection, oxidative cleavage[19] of the unmasked 1,2-dihydroxyl group, followed by $NaBH_4$-mediated reduction, provided *ent*-**5**. An-



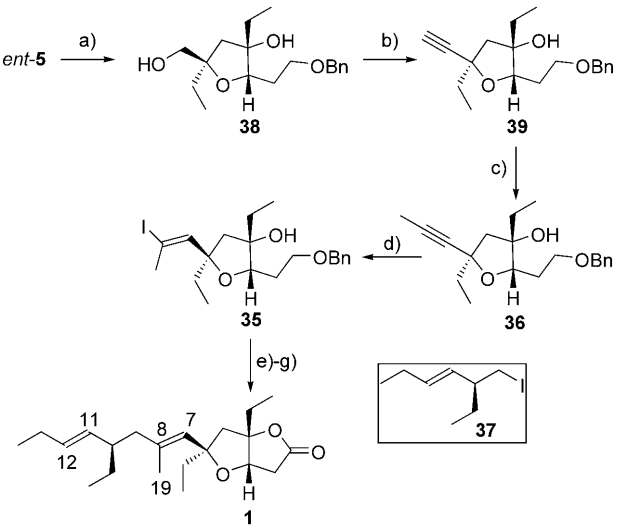
Scheme 6. Synthesis of core structure *ent*-**5**. a) *t*$BuMe_2SiCl$, imidazole, DMAP, DMF, 23°C, 24 h, 90%; b) OsO_4 (0.1 equiv), *N*-methylmorpholine *N*-oxide (NMO) (6.0 equiv), Me_2CO/H_2O (v/v = 4:1), 1 week, 23°C; c) 2,2-dimethoxypropane (4 equiv), *p*-toluenesulfonic acid (cat.), THF, 23°C, 24 h, 76% over 2 steps; d) NaH, THF, 0°C, 10 min; then CS_2, 0°C, 10 min; then MeI, 0°C, 30 min, 83%; e) *n*Bu_3SnH (10 equiv), 2,2′-azobisisobutyronitrile (AIBN) (cat.), benzene, reflux, 2 h, 90%; f) *n*Bu_4NF, THF, 23°C, 90%; g) Dess–Martin periodinane, CH_2Cl_2, 23°C, 24 h; h) $[RhCl(PPh_3)_3]$ (1.1 equiv), *p*-xylene, reflux, 60 h, 80% over 2 steps; i) 80% AcOH (aq.), 23°C, 48 h; j) $NaIO_4$ (2 equiv), H_2O, CH_2Cl_2, 23°C, 30 min; k) $NaBH_4$, EtOH, 23°C, 70% over 3 steps; l) i) diisobutylaluminum hydride (DIBAL-H), CH_2Cl_2, −78°C, 3 h; ii) MeOH, *p*-toluenesulfonic acid (cat.), THF, 23°C, overnight, 70% over 2 steps.

alytical data for synthetic *ent*-**5** were in good agreement with the reported ^1H and ^{13}C NMR spectra and specific rotation.[4a] To tolerate the subsequent reaction conditions during the connection of the central core and the side chain, ketal **27** was prepared from *ent*-**5** by partial reduction of the lactone group, followed by the formation of the cyclic ketal.

Total synthesis of compound 1 based on retrosynthetic analysis route A: With the central core *ent*-**5** (Scheme 7) and side chains **28**–**30**[20] (for the synthesis of **28**–**30**, see the Supporting Information) in hand, we turned our attention to their connection. After a number of unsuccessful experiments (Wittig olefination,[21] Julia–Kocienski olefination,[9] etc.), we realized that these failures were mainly due to the exceedingly severe steric hindrance caused by the two components. We then tried other conditions and finally found an effective addition–elimination strategy (Scheme 7). Thus, when aldehyde **31** (prepared from alcohol **27** by Swern oxidation)[12] was treated with the organolithium reagent formed from **28** by using the method devised by Yus and coworkers,[22] the two components were linked together to give a mixture of diastereomeric alcohols **32**. Compound **33** was obtained after Jones oxidation,[23] and subsequent selective reduction of the carbonyl group in **33** with $NaBH_4$ gave alcohol **34**. Several dehydration methods were investigated (sulfurane reagent,[24a] MsCl/Et_3N,[24b,c] MsCl/pyridine,[24d]



Scheme 7. a) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, 1 h, then Et_3N, −78→23 °C, 0.5 h, 75%; b) Li (10 equiv), 4,4′-di(*tert*-butyl)-1,1′-biphenyl (DTBB) (0.2 equiv), **28**, then **31**, −78 °C, THF, 3 h; c) Jones reagent, Me_2CO, 0 °C, 4 h, 30% over 2 steps; d) $NaBH_4$, EtOH, 23 °C, 1 h, 85%; e) Burgess reagent, toluene, reflux, 20 h, 60%.



Scheme 8. Total synthesis of **1**. a) i) *t*BuMe$_2$SiCl, imidazole, DMF, 23 °C, 1 h; ii) $LiAlH_4$, THF, 0 °C, 0.5 h; iii) NaH, THF, 0 °C, 0.5 h, then BnBr, reflux, 1.5 h; iv) *n*Bu$_4$NF, THF, 12 h, 23 °C, 58% over 4 steps; b) i) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, 1 h, then Et_3N, −78→23 °C, 0.5 h; ii) Bestmann's reagent, K_2CO_3, MeOH, 23 °C, 24 h, 60% over 2 steps; c) i) Me_3SiCl, imidazole, DMAP (cat.), DMF, 23 °C, 0.5 h; ii) *n*BuLi, MeOTf, THF, −78 °C, 1 h; iii) *n*Bu$_4$NF, THF, 23 °C, 5 min, 84% over 3 steps; d) i) $[PdCl_2(PPh_3)_2]$, *n*Bu$_3$SnH, *n*-hexane, 23 °C, 2 h; ii) I_2, CH_2Cl_2, 0 °C, 5 min, 60% over 2 steps; e) i) **37**, *t*BuLi, Et_2O, −78 °C, 5 min; ii) 9-methoxy-9-borabicyclo[3.3.1]nonane (9-OMe-BBN), THF, −78 °C, 10 min, then warm to 23 °C, 1 h; iii) 3 N K_3PO_4 (aq.), 3 min; then iv) **35**, $[PdCl_2(dppf)_2]\cdot CH_2Cl_2$, DMF, 23 °C, 20 h; f) Na/NH_3 (liq.), THF, −78 °C, 0.5 h; g) PDC, DMF, 23 °C, 20 h, 60% over 3 steps.

MsCl/*t*BuOK, $POCl_3$/pyridine,[24e] and *p*-toluenesulfonic acid[24f]), but all proved to be unsuccessful. Gratifyingly, when the dehydration reaction was conducted with the Burgess reagent,[24g,h] the alkene product was obtained, however, it was formed as a mixture of two chromatographically inseparable C7−C8 *E* and *Z* isomers in a ratio of 2:1, as confirmed by ^{1}H NMR spectroscopy and GC–MS.[25] We attempted to isomerize this mixture with the hope of obtaining pure *E*-compound,[26] unfortunately, the isomeric ratio remained unchanged in all trials.

Total synthesis of compound 1 based on retrosynthetic analysis route B: Because route A failed to provide pure compound **1**, we abandoned this approach and turned to route B. In this approach, we required **7** (the central core) and **8** (the side chain) as the potential Suzuki coupling precursors (Scheme 2). In practice, alkenyl iodide **35** was utilized in place of **7** due to the steric hindrance of the very compact central core, as well as the need to tolerate many harsh reaction conditions (Scheme 8). Iodide **35** could be obtained by a diastereoselective hydrostannylation reaction followed by an iodination reaction from the related alkyne **36**, which was derived from the crucial precursor *ent*-**5**.

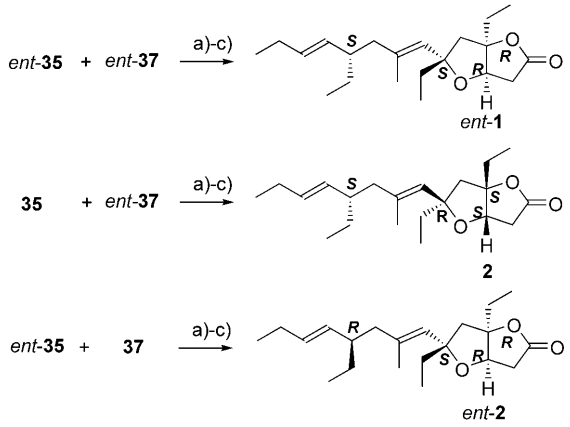
Construction of the core 35 and total synthesis of compound 1: Alkenyl iodide **35** was synthesized from *ent*-**5** by the chemical operations depicted in Scheme 8,[27] whereas the crucial boronic acid **8** could be formed in situ from iodide **37**.[28] After conversion of *ent*-**5** into **38** by a standard procedure, the resulting monocyclic alcohol **38** was converted into terminal alkyne **39** by a sequence of Swern oxidation[12] and an application of Ohira–Bestmann's modification of Seyferth–Gilbert homologation reaction.[29] Temporary protection of the tertiary hydroxyl group in **39** with a trimethylsilyl group, methylation, followed by removal of the protecting group, furnished alkyne **36** in 84% overall yield. Palladium-catalyzed hydrostannylation reactions are efficient,[30] and hexane was recently reported to inhibit the competitive stannane dimerization in coupling reactions.[30c] In light of these findings, hexane and several palladium catalysts were tested to optimize the hydrostannylation reaction of alkyne **36**. As a result of these investigations, we found that the yield could be upgraded to 80% in the presence of catalytic $[PdCl_2(PPh_3)_2]$. In this case, the diastereoselectivity was also very high and the desired stannyl compound was obtained as the only product. After iodination, the key alkenyl iodide **35** was obtained.

With the central core **35** and side chain **37** (see the Supporting Information) in hand, the Suzuki coupling reaction was performed to link the two partners together;[7] this smoothly provided the desired coupling compound as the only product. After debenzylation and PDC-mediated oxidative cyclization, compound **1** was obtained in a pure form. We were pleased to find that no isomerization reaction occurred at either the C7=C8 or the C11=C12 double bonds during the three-step route. The coupling constant between H-11 and H-12 was 15.3 Hz, indicating the *trans* stereochem-

istry of the C11=C12 disubstituted double bond. The coupling constant between H-19 (d, $J=1.4$ Hz, 3H) and H-7 (q, $J=1.4$ Hz, 1H) also led to the assignment of *E* stereochemistry to the C7=C8 trisubstituted double bond. Further information obtained from NMR spectroscopy of compound **1** helped to establish the structure of compound **1** (Scheme 8).

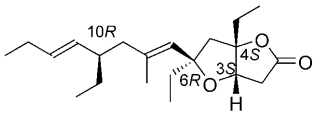
Before we completed the total synthesis of compound **1**, Semmelhack and co-workers reported a total synthesis of compound **1** based on a similar disconnection strategy.[4d] They claimed that their synthetic compound **1** had the same absolute configuration as that of the naturally occurring molecular plakortone B, based on ^{1}H and ^{13}C NMR spectral data comparison and analysis.[4d,31] However, we found that our synthetic compound **1** exhibited a different ^{1}H NMR spectrum to that obtained by Semmelhack et al., especially for the H-7 and H-11 proton resonances at $\delta=5.00$–5.08 ppm. Although the spectral data of our synthetic compound **1** was in better agreement with the ^{1}H and ^{13}C NMR spectral data of the natural plakortone B,[1] we did not wish to come to a premature conclusion regarding the configuration of the natural product, and this promoted us to synthesize the other three possible isomers of plakortone B [comparisons are summarized in the Supporting Information and in Table 1 (see below)].

Total synthesis of isomers of plakortone B (*ent*-1, 2 and *ent*-2) and the determination of its absolute configuration: With the two central cores (**35** and *ent*-**35**) and two side chains (**37** and *ent*-**37**) (for the detailed preparation of *ent*-**35** and *ent*-**37**, see the Supporting Information) available, the other three possible isomers of plakortone B were synthesized through similar sequences: Suzuki coupling, debenzylation, and oxidative cyclization reactions. All reactions proceeded smoothly to give the other three compounds (*ent*-**1**, **2** and *ent*-**2**) in high yields (Scheme 9).



Scheme 9. Total synthesis the other three isomers of plakortone B (*ent*-**1**, **2** and *ent*-**2**). a) i) **37** or *ent*-**37**, *t*BuLi, Et_2O, −78 °C, 5 min; ii) 9-BBN-OMe, THF, −78 °C, 10 min, then warm to 23 °C, 1 h; iii) 3 N K_3PO_4 (aq.), 3 min; iv) **35** or *ent*-**35**, $[PdCl_2(dppf)_2]\cdot CH_2Cl_2$, DMF, 23 °C, 20 h; b) Na/NH_3 (liq.), THF, −78 °C, 0.5 h; c) PDC, DMF, 23 °C, 20 h, 55 %-60 % in 3 steps.

All four possible isomers of plakortone B were synthesized so that a comparison of their NMR spectral data with those of the natural plakortone B could be made.[1] All ^{1}H and ^{13}C NMR spectra and specific rotation data are included in the Supporting Information, with the most crucial data summarized in Table 1. As can be seen, the four synthetic samples can be divided into two pairs of enantiomers (**1** and *ent*-**1** cf. **2** and *ent*-**2**). Although the differences in their NMR spectra were generally very small, there were considerable differences in the chemical shifts of the H-3, H-7, and H-11 proton resonances, and the differences were more distinct at $\delta=5.00$–5.08 ppm when comparing the ^{1}H NMR spectra directly. We were fortunate to obtain a copy of the original ^{1}H NMR spectrum of the natural plakortone B.[2] Whereas the ^{1}H NMR spectra of our synthetic compounds **1** and *ent*-**1** showed good agreement with that of the natural plakortone B, the ^{1}H NMR spectra of compounds **2** and *ent*-**2** exhibited significant differences (see the Supporting Information for details). It is therefore clear that **2** and *ent*-**2** are not related to the natural plakortone B. Because the specific rotation $[\alpha]_D^{25}$ of the natural plakortone B (−9.2, $c=0.72$ in $CHCl_3$)[1] differed from that of *ent*-**1** ($[\alpha]_D^{20}=+15.5$, $c=0.28$ in $CHCl_3$), this enantiomer could also be excluded. Only ^{1}H NMR spectrum and specific rotation ($[\alpha]_D^{20}=-16.0$, $c=0.39$ in $CHCl_3$) of **1** fit closely with those of the natural plakortone B.[32] These results further confirm that **1** possesses a structure that is identical to that of the natural plakortone B, so the absolute configuration of naturally occurring plakortone B can be assigned as (3*S*,4*S*,6*R*,10*R*).



plakortone B

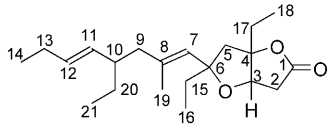
Conclusion

We have synthesized all four possible isomers of plakortone B. The absolute configuration of natural plakortone B can now be assigned as (3*S*,4*S*,6*R*,10*R*) on the basis of spectroscopic and specific rotation comparisons.

Experimental Section

All nonaqueous reactions were carried out by using oven-dried glassware under a positive pressure of dry nitrogen unless otherwise noted. All reagents and solvents were reagent grade. Further purifications and drying by standard methods were used when necessary. Except as indicated otherwise, reactions were magnetically stirred and monitored by thin-layer chromatography (TLC) using Merck Silica Gel 60 F254 plates and visualized by fluorescence quenching under UV light. In addition, compounds on TLC plates were visualized with a spray of 5 % w/v dodecamolybdophosphoric acid in ethanol, with subsequent heating. Chromatographic purification of products (flash chromatography) was performed on E.

Table 1. Specific rotation values and selected ^{1}H NMR spectral data for all four possible absolute structures of plakortone B and those of the natural product.



	Absolute configuration	Specific rotation	^{1}H NMR [ppm] H-3	H-7[a]	H-11[b]	H-12	H-19
natural plakortone B	not determined	$[\alpha]_D^{25}=-9.2$ ($c=0.72$ in $CHCl_3$)	4.21 (dd, $J=1.3$, 5.1 Hz, 1H)	5.03 (q, $J=1.3$ Hz, 1H)	5.06 (ddt, $J=1.5$, 8.4, 15.3 Hz, 1H)	5.36 (dt, $J=6.3$, 15.3 Hz, 1H)	1.69 (d, $J=1.3$ Hz, 3H)
1	3*S*,4*S*,6*R*,10*R*	$[\alpha]_D^{20}=-16.0$ ($c=0.39$ in $CHCl_3$)	4.21 (dd, $J=1.1$, 5.0 Hz, 1H)	5.03 (q, $J=1.4$ Hz, 1H)	5.06 (ddt, $J=1.0$, 8.4, 15.3 Hz, 1H)	5.36 (dt, $J=6.3$, 15.3 Hz, 1H)	1.69 (d, $J=1.4$ Hz, 3H)
ent-**1**	3*R*,4*R*,6*S*,10*S*	$[\alpha]_D^{20}=+15.5$ ($c=0.28$ in $CHCl_3$)	4.21 (dd, $J=1.2$, 5.0 Hz, 1H)	5.03 (s, 1H)	5.06 (dd, $J=7.8$, 15.3 Hz, 1H)	5.36 (dt, $J=6.3$, 15.3 Hz, 1H)	1.69 (d, $J=1.1$ Hz, 3H)
2	3*S*,4*S*,6*R*,10*S*	$[\alpha]_D^{20}=-30.1$ ($c=0.41$ in $CHCl_3$)	4.19 (dd, $J=1.5$, 4.8 Hz, 1H)	5.04 (s, 1H)	5.05 (dd, $J=8.8$, 15.3 Hz, 1H)	5.36 (dt, $J=6.3$, 15.2 Hz, 1H)	1.69 (d, $J=1.7$ Hz, 3H)
ent-**2**	3*R*,4*R*,6*S*,10*R*	$[\alpha]_D^{20}=+29.5$ ($c=0.67$ in $CHCl_3$)	4.19 (dd, 1H, $J=1.5$, 4.8 Hz, 1H)	5.04 (s, 1H)	5.05 (dd, $J=8.8$, 15.3 Hz, 1H)	5.36 (dt, $J=6.3$, 15.2 Hz, 1H)	1.69 (d, $J=1.7$ Hz, 3H)

[a] ^{1}H NMR spectra of compounds **1**, *ent*-**1**, **2** and *ent*-**2** were recorded with a Bruker Avance III-400 spectrometer. Coupling constants *J*(H19,H7) and *J*(H7,H19) of **1** were determined by 2D *J*-Resolved NMR spectroscopic analysis with an Avance Bruker 600 MHz spectrometer. Due perhaps to the resolution of the NMR equipment used, H-7 of our synthetic samples (*ent*-**1**, **2** and *ent*-**2**) showed as a singlet in the ^{1}H NMR spectra; the signal from H-19 gave a doublet. [b] For the same reason as stated in [a], H-11 of our synthetic samples (*ent*-**1**, **2** and *ent*-**2**) showed a 'dd' peak instead of a 'ddt' set.

Merck Silica Gel 60 (230–400 mesh). All evaporation of organic solvents were carried out with a rotary evaporator. Yields refer to chromatographically and spectroscopically pure compounds, unless otherwise stated.

NMR spectra were recorded with a Bruker DRX300 spectrometer, a Bruker Avance III 400 spectrometer or an Avance Bruker 600 MHz spectrometer. Chemical shifts (δ) are reported in ppm with the solvent resonance given relative to chloroform ($\delta=7.26$ ppm) or tetramethylsilane ($\delta=0.00$ ppm) for ^{1}H nuclei, and chloroform ($\delta=77.0$ ppm) for ^{13}C nuclei. Data are reported as follows: brs=broad singlet, s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet; coupling constants in Hz. ^{1}H NMR measurements were carried out at RT in deuterated chloroform unless otherwise stated. Mass spectra (EIMS and HRMS (ESI)) were obtained with a HP 5989B spectrometer and determined at an ionizing voltage of 70 eV unless otherwise stated; relevant data are tabulated as *m*/*z* values.

Melting points were measured on a Reichert Microscope apparatus and were uncorrected. Optical rotations were measured with a Perkin–Elmer model 241 polarimeter operating at the sodium D line with a 100 mm path-length cell operating at 20 °C, and are reported as follows: $[\alpha]_D^T$ concentration (g/100 mL), and solvent. X-ray data sets were obtained with a P4 X-ray four circle diffractometer and analyzed with SHELXTL PLUS (PC Version) unless otherwise stated.

For full experiment details concerning all new compounds, see the Supporting Information.

Vinyl iodide 35: Compound **36** (65 mg, 0.206 mmol) and $[PdCl_2(PPh_3)_2]$ (0.01 mmol, 3 mg) were added to a 10 mL, argon-filled, two-necked, round-bottomed flask equipped with a magnetic stirring bar. The flask was evacuated and filled with argon three times, and then freshly distilled *n*-hexane (3 mL) was added by using a syringe. Tributyltin hydride (140 μL, 151 mg, 0.5 mmol) was added slowly (over about 10 min) by using a syringe. The reaction was stirred at 23 °C for 1.5 h, then immediately transferred to a silica gel column (8 g) and rapidly eluted with hexanes until the excess $Bu_3SnH/(Bu_3Sn)_2$ was removed, followed by elution with a mixture of hexanes and ethyl acetate (10:1) to obtain the stannane compound as a colorless oil: $R_f=0.23$ (hexanes/ethyl acetate, 10:1).

The obtained stannane compound was dissolved in CH_2Cl_2 (4 mL) and cooled to 0 °C. I_2 (50 mg, 0.196 mmol) was added and the resulting mixture was stirred at 0 °C for 5–8 min then worked up by the addition of a saturated aqueous solution of $Na_2S_2O_3$ (3 mL) and extracted with diethyl ether (3×10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue that was purified by flash column chromatography on silica gel (8 g, hexanes/ethyl acetate, 5:1) to give **35** (55 mg, 60% for the 2 steps) as an oil. $R_f=0.20$ (hexanes/ethyl acetate, 5:1); $[\alpha]_D^{20}=-19.3$ ($c=0.8$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): $\delta=7.25$ ppm (m, 5H; ArH), 5.98 (s, 1H; =CH), 4.42 (s, 2H; $ArCH_2$), 3.56–3.63 (m, 2H; OCH_2), 3.45–3.49 (m, 1H; OCH), 2.50 (s, 3H; $=CCH_3$), 2.28 (s, 1H; OH), 1.95 (d, ^3J(H,H)=13.2 Hz, 1H; CH), 1.82 (d, ^3J(H,H)=13.2 Hz, 1H; CH), 1.83–1.89 (m, 2H; CH_2), 1.50–1.59 (m, 1H; CH), 1.45–1.55 (m, 2H; CH_2), 1.31–1.39 (m, 1H; CH), 0.86 (t, ^3J(H,H)=6.8 Hz, 3H; CH_3), 0.83 ppm (t, ^3J(H,H)=6.5 Hz, 3H; CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): $\delta=146.1$ (=CH), 137.9 (Bn), 128.6 (Bn), 127.9 (Bn), 127.8 (Bn), 96.3 (=CI), 86.2 (COH), 82.6 (COCH), 81.2 (CHOC), 73.3 ($PhCH_2$), 67.4 (CH_2OBn), 50.9 (CH_2), 34.7 (CH_2), 30.9 (CH_2), 29.5 (CH_3C=C), 29.3 (CH_2), 9.1 (CH_3), 8.8 ppm (CH_3); HRMS (ESI): *m*/*z* calcd for $C_{20}H_{29}O_3INa$: 467.1054 $[M+Na]^+$; found: 467.1052.

Compound 1: Iodide **37** (50 mg, 0.21 mmol) was added to a 25 mL oven-dried, two-necked, round-bottomed flask under an argon atmosphere. Diethyl ether (3 mL) was added by using a syringe, and the resulting solution was cooled to −78 °C. *t*BuLi (0.4 mL, 1.5 M in pentane, 0.6 mmol) was added rapidly by using a syringe and the solution was stirred at −78 °C for 5 min, then 9-methoxy-9-borabicyclo[3.3.1]nonane (0.5 mL, 1 M in THF, 0.5 mmol) was added by using a syringe followed by THF (3 mL). The solution was stirred at −78 °C for 10 min, then slowly warmed to 23 °C and stirred at that temperature for 1 h. An aqueous solution of K_3PO_4 (0.17 mL, 3 N, 0.51 mmol) was added followed by a solution of vinyl iodide **35** (23 mg, 0.065 mmol) in THF (1 mL), DMF (3 mL), and $[PdCl_2(dppf)_2]\cdot CH_2Cl_2$ (0.006 mmol, 5 mg). The resulting black solution was stirred at 23 °C for 16 h. Diethyl ether (10 mL) was added and the mixture was transferred to a separating flask. Water (10 mL) was added and the layers were separated. The aqueous layer was extracted

with diethyl ether (3×10 mL). The combined organic extracts were washed with water (2×10 mL) and brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give a residue that was purified by flash column chromatography on silica gel (8 g; hexanes/ethyl acetate, 10:1) to give the coupling product as a colorless oil that was used immediately in the following debenzylation reaction. $R_f = 0.25$ (hexanes/ethyl acetate, 10:1).

A 50 mL three-necked, round-bottomed flask was equipped with a magnetic stirring bar and attached to a vacuum line, an oil bubbler, and a tank of anhydrous ammonia. The flask was placed under vacuum, filled with argon, and cooled to −78 °C. The argon flow was stopped and ammonia flow was condensed. When 5–6 mL liquid ammonia condensed into the flask, the ammonia flow was stopped, the tank and bubbler were disconnected and the flask was placed under argon. Sodium (90 mg, 3.9 mmol) was cut into small pieces, washed quickly with anhydrous diethyl ether to remove any residual oil, and added in portions to the flask at −78 °C. The liquid turned a deep-blue color and was stirred at −78 °C for 10 min until all of the sodium had been dissolved. A solution of the above coupling product in THF (10 mL) was added by using a syringe and the mixture was stirred at −78 °C (blue color persists) for 45 min. NH_4Cl (535 mg, 10 mmol) was added and the solution was stirred at −78 °C until the blue color disappeared. The flask was opened to air and warmed to 23 °C to allow ammonia to evaporate. Water (10 mL) and diethyl ether (30 mL) were added, the organic layer was separated and the aqueous layer was extracted with diethyl ether (3×10 mL). The combined organic extracts were washed with water (10 mL) and brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give a residue that was purified by flash column chromatography on silica gel (8 g; hexanes/ethyl acetate, 2:1) to afford the debenzylation product as a colorless oil, which was immediately used in the following oxidative cyclization reaction: $R_f = 0.23$ (hexanes/ethyl acetate, 2:1).

PDC (150 mg, 0.4 mmol) at 0 °C was added in one portion to a solution of the debenzylation product in DMF (1.5 mL) and the reaction mixture was stirred at 23 °C overnight. The mixture was diluted with diethyl ether (30 mL) then washed with water (2×10 mL) and brine (10 mL). The organic phase was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give a residue that was purified by flash column chromatography on silica gel (8 g; hexanes/diethyl ether, 10:1) to give compound **1** as a colorless oil (13 mg, 60% over 3 steps). $R_f = 0.23$ (hexanes/diethyl ether, 10:1). $[\alpha]_D^{20} = -16.0$ ($c = 0.39$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 5.36$ (dt, ^3J(H,H) = 6.3, 15.3 Hz, 1H; =CH), 5.06 (ddt, ^3J(H,H) = 1.0, 8.4, 15.3 Hz, 1H; =CH), 5.03 (q, ^3J(H,H) = 1.4 Hz, 1H; =CH), 4.21 (dd, ^3J(H,H) = 1.1, 5.0 Hz, 1H; OCH), 2.71 (dd, ^3J(H,H) = 5.1, 18.6 Hz, 1H; COCH), 2.64 (dd, ^3J(H,H) = 1.1, 18.6 Hz, 1H; COCH), 2.24 (d, ^3J(H,H) = 13.7 Hz, 1H; CH), 2.14 (d, ^3J(H,H) = 13.7 Hz, 1H; CH), 1.99–2.04 (m, 4H; 2CH, CH_2), 1.82–1.87 (m, 1H; CH), 1.69 (d, ^3J(H,H) = 1.4 Hz, 3H; CH_3), 1.66–1.77 (m, 4H; $2CH_2$), 1.32–1.38 (m, 1H; CH), 1.10–1.17 (m, 1H; CH), 0.96 (t, ^3J(H,H) = 7.2 Hz, 3H; CH_3), 0.95 (t, ^3J(H,H) = 7.4 Hz, 3H; CH_3), 0.86 (t, ^3J(H,H) = 7.4 Hz, 3H; CH_3), 0.83 ppm (t, ^3J(H,H) = 7.4 Hz, 3H; CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 175.7$ (C=O), 137.1 (=C), 132.7(=CH), 131.9 (=CH), 129.5 (=CH), 97.2 (COC=O), 86.9 (COCH), 79.5 (CHOC), 49.0 (CH_2), 46.9 (CH_2C=C), 42.6 (CHC=C), 36.7 (CH_2C=O), 33.7 (CH_2), 30.3 (CH_2), 27.8 (CH_2), 25.5 (CH_2), 16.7 (CH_3C=C), 14.0 (CH_3), 11.5 (CH_3), 8.7 (CH_3), 8.3 ppm (CH_3); HRMS (ESI): m/z $[M+Na]^+$ calcd $C_{21}H_{34}O_3Na$: 357.24000; found: 357.24002.

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[31] In his article, Professor Semmelhack did not report the specific rotation of their synthetic **1**, and the ^{1}H NMR spectrum obtained by his group showed a slight difference at $\delta = 5.00$–5.08 ppm as compared with the authentic ^{1}H NMR spectrum of **1** provided by Professor Ernesto Fattorusso.

[32] The specific rotation of our synthetic **1** $[\alpha]_D^{20} = -16.0$ ($c = 0.39$ in $CHCl_3$) does not quite agree with that of the naturally occurring plakortone B $[\alpha]_D^{20} = -9.2$ ($c = 0.72$ in $CHCl_3$). However, it is envisaged that this difference between synthetic **1** and the natural plakortone B was acceptable because 1) synthetic **1** could fit the spectral data of natural plakortone B; 2) the specific rotation value of synthetic **1** is in good agreement with the value of its synthetic enantiomer *ent*-**1** $[\alpha]_D^{20} = +15.5$ ($c = 0.28$ in $CHCl_3$); and 3) the difference might be due to the way these values were measured, for example, purity, equipment, temperature, and concentration of the samples.

[33] CCDC-763045 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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