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Spirodionic Acid, a Novel Metabolite from *Streptomyces* sp., Part 2: Total Synthesis through a Twofold Michael Addition as a Selective Spiroannelation Strategy**

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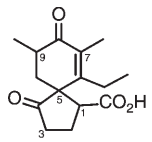
Dedicated to Professor Lutz F. Tietze on the occasion of his 65th birthday

Abstract: To elucidate the structure of the new natural product spirodionic acid, which has three stereogenic centers of hitherto unknown configuration, two 4-ethenylspiro[4.5]dec-6-en-1,8-diones with opposite relative configuration at C4 and C5 were prepared. The first access involved the synthesis of 3-ethenyl-2-formylcyclopentanone (**8**) using a three-component coupling process. A sequence of Michael addition to penten-3-one (**7**) and intramolecular aldol condensation then led to the highly selective formation of the 4*S**,5*S**-configured spirocycle **5**. In contrast, a selective spiroannelation of a cyclohexenone ring was accomplished by a novel type of twofold Michael addition to the dialkenyl ketone **11** with subsequent dehydrogenation to furnish the 4*S**,5*R**-configured spirocycle **25**. Diastereoselective methylation and oxidative degradation then completed a highly efficient synthesis of the natural product as prerequisite for the assignment of its absolute configuration.

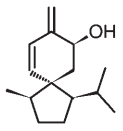
Keywords: Michael addition · natural products · ring annelation · spiro compounds · total synthesis

Introduction

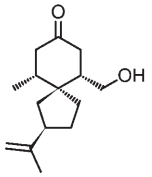
Recently, the new secondary metabolite spirodionic acid (**1**) was isolated from *Streptomyces* sp. by Grond and co-workers and its constitution derived from spectroscopic analyses (Scheme 1).[1] Despite the rather small size of this compound, it still has an interesting structure that features three stereogenic centers and a high density of functional groups and substituents on its purely carbocyclic spiro[4.5]decene skeleton. However, neither the absolute nor the relative configuration could be deduced from the isolated natural product. Regarding the biosynthesis, it was shown that this compound is formed by a rarely occurring enzymatic Diels–Alder-type reaction that presumably employs the well-known cytotoxic metabolite sarkomycin, which was used in cancer treatment in the 1960s and still attracts a lot of interest in synthetically oriented groups,[2] as a dienophile.[3] Yet, no significant biological activity of spirodionic acid has been found so far, which is in part a result of its limited availability because of the poor productivity of the producing strain and a tedious isolation procedure. Thus, a total synthesis of the metabolite is desirable to be able to both elucidate which of the eight possible stereoisomers of constitution **1** is



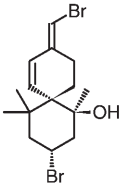
Spirodionic acid (**1**)



4(15),5-Acoradien-3-ol (**2**)



14-Hydroxy-11-spirovetiven-2-one (**3**)



9,15-Dibromo-1,3(15)-chamigradien-7-ol (**4**)

Scheme 1. Structures of spirodionic acid (**1**) and spirocyclic sesquiterpenes.

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[**] For Part 1, see: ref. [1].

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the naturally occurring isomer and to generate sufficient amounts of the natural product for biological testing.

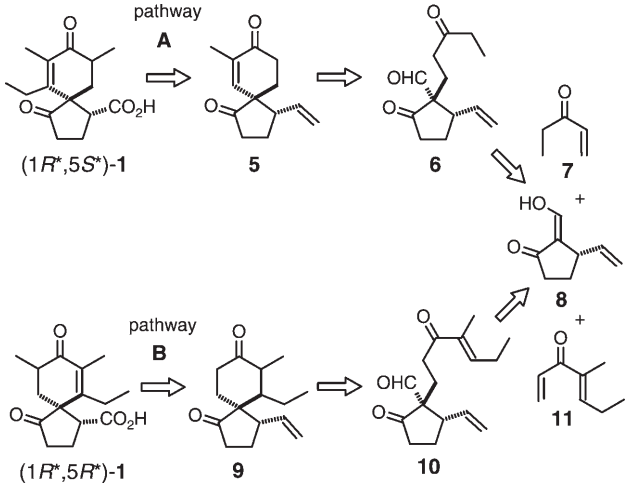
The main challenge in the preparation of chiral spirocyclic compounds is the efficient assembly of the stereogenic spiro carbon center in a stereoselective manner. Yet, the occurrence of spirocyclic skeletons in a number of natural products, such as the sesquiterpenes of the spirovetivane, acorane, and chamigrane classes (e.g., **2**–**4**),[4] has led to extensive efforts to solve this synthetic problem.[5] Herein, we report the total synthesis of spirodionic acid, including a novel selective spiroannelation of a cyclohexenone ring by a twofold Michael addition.

Retrosynthetic analysis: In view of the unknown configuration of the natural product, the envisioned synthetic strategy would have to promise a high and predictable stereoselectivity and at the same time would have to allow a flexible approach to the different stereoisomers. Many of the reported methods for stereoselective spirocyclizations use the directing influence of a substituent on an adjacent stereogenic carbon center for stereocontrol.[6] These techniques include the Diels–Alder reaction of 3-alkyl-2-methylenecyclopentanones with isoprene—a concept that corresponds to a biomimetic synthesis of spirodionic acid—yet the alkyl group induced only a moderate diastereoselectivity of 2.6:1 with a favored attack of the diene on the opposite face of the five-membered ring.[6b] In contrast, a high diastereoselectivity has been achieved in the spiroannelation of cyclohexenone rings by a sequence comprising a Michael addition and an intramolecular aldol reaction with cyclopentanecarbaldehydes, or their enamines, as Michael donors and α,β-unsaturated ketones as Michael acceptors.[7]

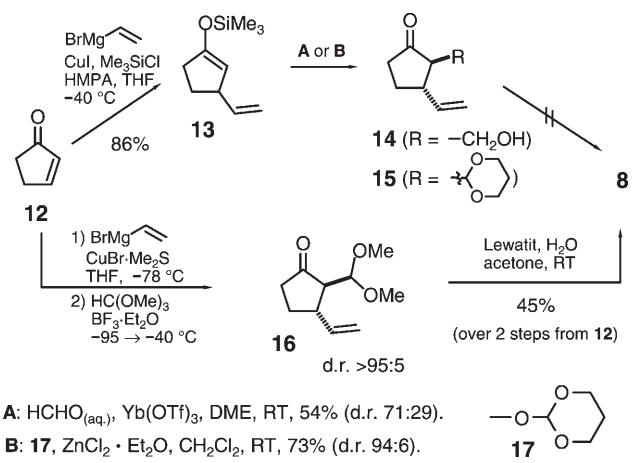
Thus, it was expected that the spiro[4.5]decenedione **5** with a *cis* orientation of the vinyl substituent and the alkenyl side of the six-membered ring, which ought to be a precursor for the 1*R**,5*S**-stereoisomer of **1**, could be obtained by an intramolecular aldol condensation of cyclopentanone derivative **6** (Scheme 2). This compound would stem from the Michael addition of the 2-hydroxymethylenecyclopentanone **8** to penten-3-one (**7**), which should occur at the face opposite to the vinyl substituent at C3 of the five-membered ring and thus determine the selectivity (pathway A). A pathway involving a twofold Michael addition as the key step was envisaged for the synthesis of the 1*R**,5*R**-stereoisomer of **1** with a *trans* relationship of the carboxy moiety and the alkenyl side of the six-membered ring. Thus, the same cyclopentanone derivative **8** would be employed in a Michael addition, yet using the dialkenyl ketone **11** as an acceptor. This enolate addition was thought to occur preferentially at the sterically less hindered β carbon atom of the dienone **11** to furnish **10**. 2-Formylcycloalkanones are in general quite unstable molecules that readily undergo deformylation. In the case of **10**, this mostly undesirable behavior should lead to the regioselective formation of an enolate that could undergo a second, now intramolecular, Michael addition, thus resulting in a 6-*endo-trig* cyclization to afford the spiro[4.5]decanedione **9**. Once again, the directing effect of the vinyl moiety at C3 should favor the bond formation with *trans* selectivity, yet this now leads to the spirocycle with opposite relative configuration at C1 and C5 relative to pathway A.

Results and Discussion

Towards the shared starting material **8** for both pathways cyclopent-2-enone (**12**) was transformed in a Cu-catalyzed, chlorotrimethylsilane-accelerated[8] 1,4-addition to yield the silyl enol ether **13** (Scheme 3). A Mukaiyama-type aldol reaction with formaldehyde in aqueous solution then afforded the 2-hydroxymethylcyclopentanone **14**.[9] Alternatively, the dialkoxymethyl derivative **15** was obtained by treatment of **13** with 2-methoxy-1,3-dioxane (**17**) in the presence of $ZnCl_2$.[10] Yet on the one hand, attempted oxidation of **14** to give the desired product **8** with the Dess–Martin periodane or activated dimethyl sulfoxide (DMSO) only led to decom-



Scheme 2. Retrosynthetic considerations concerning spirodionic acid (**1**).



Scheme 3. Synthesis of the starting materials for the Michael additions. DME = 1,2-dimethoxyethane, HMPA = hexamethylphosphoric acid triamide.

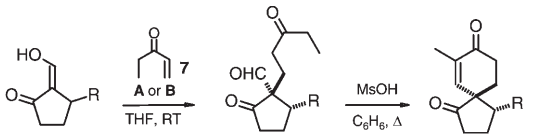
position, whereas on the other hand, acid-catalyzed hydrolysis of the 1,3-dioxane moiety in **15** only occurred under quite harsh conditions with concomitant deformylation to give 3-ethenylcyclopentanone. Therefore, the dimethoxy acetal **16** was prepared in a one-pot procedure starting from **12**. Careful modification of the general protocol developed by Noyori and co-workers[11] for the first step of this type of three-component coupling (original conditions: CuI, P*n*Bu$_3$, and RLi in Et$_2$O) resulted in preparation of the rather unstable acetal **16** in good yield. The crude product was directly subjected to mild hydrolysis conditions by using an acidic cation-exchange resin[12] to furnish the 2-formylcyclopentanone **8** in an overall yield of 45%.

The spiroannelation of cyclohexenone rings by using a Michael addition and subsequent aldol reaction (pathway A) has been achieved with both plain cycloalkanecarbaldehydes[7c] that is, compounds without a carbonyl moiety adjacent to the future spiro carbon, and 2-formylcycloalkanones.[13] The second carbonyl moiety in the latter compounds in principle facilitates the 1,4-addition, yet, at the same time it eases the deformylation, thus leading to undesirable reaction modes. Thus, a thorough adjustment of the reaction conditions is frequently indispensable. In particular, the second step of this sequence, the cyclizing aldol condensation, has been described under both alkaline and acidic conditions. However, typically the use of KOH only resulted in good yields when starting from cycloalkanecarbaldehydes.[6c] Tricarbonyl derivatives related to **6** were mainly cyclized with catalytic amounts of sulfonic acids in benzene at reflux,[13e] even though Whitehurst and Dave reported rapid deformylations under these conditions.[13b]

Therefore, the desired spiroannelation towards **5** was initially studied with the unsubstituted 2-formylcyclopentanone (**8H**) as a model substrate. Transformation of this compound with penten-3-one (**7**) in the presence of a catalytic amount of KOH furnished the tricarbonyl compound **6H** in 61% yield (Table 1, condition A), whereas the use of catalytic amounts of NEt$_3$ and 1,8-diazabicyclo[4.5]undec-7-ene (DBU) as bases raised the yield to 88% (condition B). The aldol condensation then smoothly occurred upon heating **6H** with a small amount of methanesulfonic acid (MsOH) to give the spirodecenedione **5H** in high yield.

The advantage of applying amines as bases in the Michael addition became even more evident on treatment of the actual substrate **8** with enone **7**. None of the desired product **6** was obtained in the presence of KOH (condition A), and the diastereomerically pure dicarbonyl **18**, which arises from the Michael addition and subsequent deformylation, was the only identified product. In contrast, **6** was isolated in 75% yield under condition B. The vinyl substituent in the starting material **8** indeed exerted a directing influence that led to a good diastereoselectivity of 90:10 in this transformation. Lowering the reaction temperature to 0°C did not lead to an increased diastereomeric ratio, yet the attained selectivity corresponds approximately to the selectivities obtained in previously reported examples. Thus, in comparable reactions, a vicinal methyl substituent on a five- or six-membered ring induced a selectivity of 80:20[6g] or 90:10,[7a] respectively, whereas the bulky isopropyl substituent on a five-membered ring led to selectivities exceeding 92:8.[6g,7b,c]

Table 1. Assembly of the spiro[4.5]decene skeleton through a Michael addition and subsequent intramolecular aldol condensation.



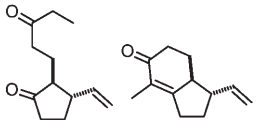
8-H (R = H)
8 (R = vinyl)

6-H (R = H)
6 (R = vinyl, d.r. 90:10)

5-H (R = H)
5 (R = vinyl, d.r. 90:10)

Starting material	Conditions[a]	Product	Yield [%]
8H	A	**6H**	61
8H	B	**6H**	88
6H	–	**5H**	81
8	A	**18**	21
8	B	**6**	75
6	–	**5**[b]	38

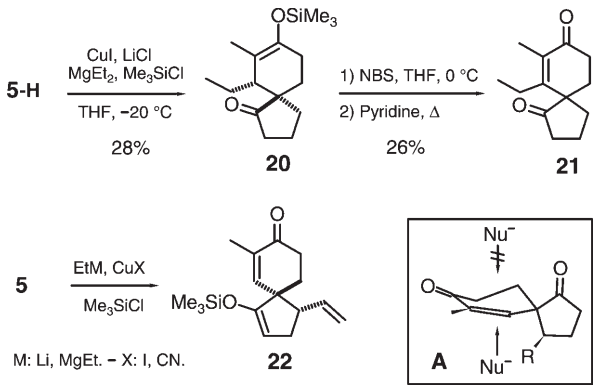
[a] A: KOH; B: NEt$_3$ and DBU. [b] An additional 21% of **19** was obtained.



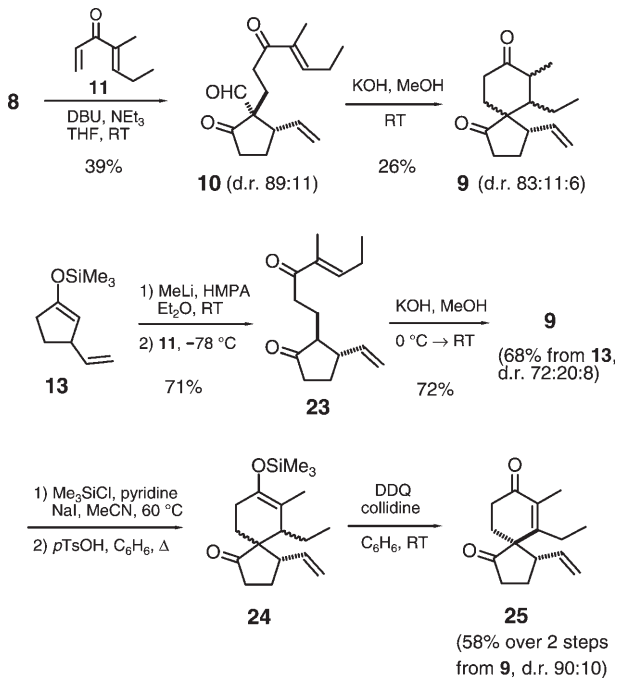
18 **19**

The aldol condensation of this 90:10 mixture of diastereomeric **6** under the same acidic conditions as described above afforded two separable diastereomeric spirocycles in the same ratio. The yield of the desired product **5** was only moderate as a result of deformylation, as disclosed by isolation of the bicyclo[4.3.0]nonene derivative **19**, formed by an overall Robinson annelation of **8** with deformylation. This apparently lower stability of the vinyl-substituted compounds might be due to their increased steric congestion. Even treatment of **6** with pyrrolidinium acetate (that is, under typical Knoevenagel conditions, which worked well in the spirocyclization of other sterically congested systems),[13c,d,g] only resulted in deformylation to the cyclopentanone **18**.

The total synthesis of **1** along pathway A should be continued with the introduction of the ethyl substituent at C6 (numbering of spirodionic acid). For the model substrate **5H**, this transformation could be accomplished by a cuprate 1,4-addition, which gave best results according to a protocol of Reetz and Kindler[14] for sterically encumbered enones (Scheme 4). The silyl enol ether **20** was obtained in 28% yield (38% based on 73% conversion) as a single diastereomer. Bromination of this compound and subsequent dehydrobromination then led to the spiro[4.5]decenedione **21** in 26% yield without optimization. Yet, all attempts to perform the analogous transformation with the vinyl-substituted spiro[4.5]decene **5** failed and just led to the silyl enol ether **22**. Obviously, the approach of the cuprate in **5** and **5H** cannot occur on the *Si* face of the cyclohexenone ring to which the carbonyl moiety of the five-membered ring is



Scheme 4. Studies on cuprate 1,4-addition reactions on spiro[4.5]decenes **5** and **5H**. M = metal, NBS = *N*-bromosuccinimide, Nu = nucleophile.



Scheme 5. Spiroannelation of a cyclohexenone ring onto a cyclopentanone by twofold Michael addition and subsequent dehydrogenation.

pointing (upper face in illustration A). In the case of **5H**, the addition should therefore take place on the opposite face and furnish the silyl enol ether **20** of shown relative configuration, whereas the vinyl substituent in **5** also sterically blocks this addition.

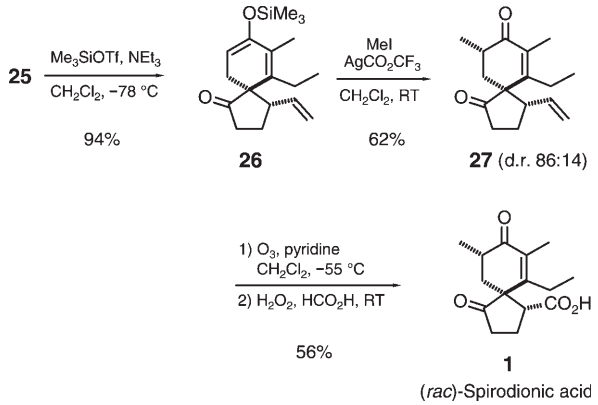
Parallel to these efforts, the spiroannelation by sequential twofold 1,4-addition (pathway B in Scheme 2) was investigated. Multifold Michael additions involving a reversal of donor and acceptor sites during the sequence have been used as versatile tool in a number of syntheses.[15] However, the assembly of cyclohexanone rings with dialkenyl ketones as twofold Michael acceptors is less developed.[16] In most reports, dibenzylideneacetone, or derivatives thereof, were treated with symmetrical 1,3-dicarbonyl compounds, such as cyclohexa-1,3-dione or malonic acid derivatives, as twofold Michael donors. Only a few examples that employ either chiral enolates as Michael donors[16d,h] or nonsymmetrical dialkenyl ketones[16c,g,i,j,l] are known, but none that combines these two features. The required dialkenyl ketone **11** was readily obtained by oxidation with MnO_2 of the respective alcohol, which in turn was prepared by 1,2-addition of vinylmagnesium bromide to the aldol condensation product of propionaldehyde. The first Michael addition of the 2-formylcyclopentanone **8** to this acceptor was performed under the already optimized conditions and gave the desired product **10** with essentially the same diastereoselectivity as the analogous transformation using pentenone **7** (compare Scheme 5 and Table 1). Although the reaction occurred with complete regioselectivity at the sterically less encumbered vinyl group of the acceptor, the yield was only 39% as a result of partial decomposition upon chromatographic purification. Treatment of **10** with an excess of KOH then led to the intended deformylation and concomitant cyclizing Michael addition to give the spiro[4.5]decanedione **9** as a mixture of three diastereomers, yet the yield was disappointingly low because of intermolecular side reactions.

Better results were obtained without the formyl group in the substrate. Thus, the silyl enol ether **13** was cleaved with methyllithium to yield the corresponding lithium enolate, which smoothly underwent the first Michael addition to **11** at −78 °C to furnish **23** with complete regioselectivity, concerning both the Michael donor and the acceptor, and complete diastereoselectivity. Even without directed enolate formation by deformylation, as in the case of **10**, but under equilibrium conditions, the intramolecular Michael addition of substrate **23** exclusively gave the spiroannelated product **9** and none of the corresponding bicyclo[5.2.1]decanedione, which would be formed by a Michael addition involving the regioisomeric cyclopentanone enolate. In view of the steric constraints around the spiro carbon atom in **9**, this selectivity is noteworthy even though the closure of a six-membered ring is generally faster than that of an eight-membered ring.[17] Good yields were thus achieved in both steps (71 and 72%, respectively), and the overall yield was even increased to 68% when intermediate **23** was not purified.

The spiro[4.5]decanedione **9** was obtained as a 72:20:8 mixture of the same three diastereomers as before. The relative configurations of these stereoisomers were not analyzed any further, as two of the four stereogenic centers in **9** will be eliminated in the next step, the introduction of the double bond between C6 and C7. After several methods for such a selective dehydrogenation had met with no success,[18] **9** was treated with the highly reactive iodotrimethylsilane, prepared in situ.[19a] The thus-obtained mixture of different silyl enol ethers underwent equilibration under acidic conditions[19b] to predominantly give the desired regioisomer **24**. Without purification, this compound was subjected to oxidation with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) in the presence of collidine to avoid premature hydrolysis of the enol ether by an acidic hydroquinone species,[20] and the spiro[4.5]decenedione **25** was isolated in 58% yield over the

two steps from **9**. The 90:10 ratio of the two diastereomers of **25**, which are separable by repeated column chromatography or preparative HPLC, proves that the second, intramolecular Michael addition (**23**→**9**) must have occurred with good diastereoselectivity as well. Altogether, this sequence represents a selective spiroannelation of a cyclohexenone ring onto a cyclopentanone in 39% yield. A related transformation, yet obtained in just one step, was accomplished by Stork and Tomasz, who carried out a twofold Michael addition onto an acetylenic enone; however, the yield was only 4%.[21]

With the spiro[4.5]decendione **25** in hand, the total synthesis of **1** would be completed by methylation at C9, thus introducing the third stereogenic center, and the transformation of the vinyl unit into a carboxy group. The methylation was attempted relying on substrate-controlled diastereoselectivity; however, this approach still required a differentiation of the three possible reaction sites. Once more, a number of different strategies was examined[18] and again, the selective formation of a silyl enol ether was the method of choice. Starting from diastereomerically pure (4*S**,5*R**)-**25**, the reaction with trimethylsilyl triflate (TMSOTf) at low temperature furnished the enol ether **26** in almost quantitative yield (Scheme 6). Treatment with methyl iodide in the presence of silver salts as activating agents[22] led to the desired product **27** in 62% yield (99% based on 37% re-isolated **25**) with a diastereomeric ratio of 86:14. The preferred formation of one diastereomer, which later on was assigned to have a 4*S**,5*R**,9*S** configuration based on the X-ray structure analysis of a succeeding product, must be caused by kinetic control, as erosion of the diastereomeric ratio was observed when **27** was stored in [D_4]MeOH in the presence of a catalytic amount of sodium methoxide. At last, the vinyl substituent in **27** was oxidatively degraded by selective ozonolysis in the presence of pyridine, which causes an increased selectivity for the transformation of electron-rich double bonds.[23] Oxidative work-up of the thus-obtained ozonides then furnished the desired compound **1** in 56% yield along with small amounts of uncleaved, remarkably stable ozonides. Even though the 86:14 mixture of **27** was employed, the carboxylic acid **1** was obtained as a single diastereomer.



Scheme 6. Completion of the total synthesis of *rac*-spirodionic acid (**1**).

It is therefore suspected that the isolated ozonides might stem from the minor diastereomer of **27**. Comparison of the spectroscopic properties of synthetic **1** with those of spirodionic acid isolated from *Streptomyces* and NMR experiments of mixtures of synthetic **1** and the natural product proved that they were identical. Thus, the total synthesis using a twofold Michael addition as a key step for the spiroannelation of the cyclohexenone ring yielded the correct diastereomer on the first attempt. The resolution of the racemic synthetic compound could be accomplished by formation of the diastereomeric camphorsultam amides with (1*S*,5*R*,7*R*)-10,10-dimethyl-3λ^6-thia-4-azatricyclo[5.2.1.$0^{1,5}$]decane 3,3-dioxide and fractionating crystallization.[1] At the same time this approach furnished crystals suitable for X-ray diffraction analysis that proved the 1*R*,5*R*,9*S* configuration of the natural spirodionic acid.

Conclusion

Based on essentially the same starting material and using the concept of substrate-controlled diastereoselectivity, 4-ethenylspiro[4.5]dec-6-ene-1,8-diones with opposite relative configurations at C4 and C5 were prepared by either a sequence of a Michael addition and an aldol condensation or a twofold Michael addition and subsequent dehydrogenation. The first method has also been proven to be useful in other syntheses, yet has the inherent problem of readily occurring deformylations that lead to Robinson instead of spiroannelations. In addition, unpredictable difficulties emerged in the attempted subsequent transformation of the thus-obtained spiro[4.5]decenedione **5** into the target structure **1**. Thus, this compound is another example of a structure for which the synthesis appears to be fairly straightforward at first glance, yet is hampered by a very specific spatial arrangement of substituents and functional groups.

In contrast, the second method furnished very good results concerning both yield and selectivity. The novelty and special feature of this approach is the combination of the highly efficient formation of quaternary spiro carbon centers by a twofold Michael addition to a dialkenyl ketone with effective stereocontrol exerted by a vicinal stereogenic carbon center in the Michael donor. This approach leads to a selective spiroannelation of a highly substituted cyclohexanone moiety. From there, careful investigation of the subsequent steps towards spirodionic acid (**1**) led to an efficient completion of its synthesis without any need for protection and deprotection steps along the whole route. Thus, the new natural product **1** was prepared in racemic form from cyclopent-2-enone in eight steps with 10% overall yield. Work towards an enantioselective synthesis of spirodionic acid and the application of this novel spiroannelation methodology towards other synthetic goals is now in progress.

Experimental Section

General: ^{1}H NMR spectra were recorded on a Bruker AM 250 (250 MHz) spectrometer. Chemical shifts in $CDCl_3$ are reported as δ values relative to $CHCl_3$ ($\delta = 7.26$ ppm) as the internal reference unless stated otherwise. ^{13}C NMR spectra were recorded on a Bruker AW 250 (62.9 MHz) spectrometer. Chemical shifts in $CDCl_3$ are reported as δ values relative to $CDCl_3$ ($\delta = 77.0$ ppm); the multiplicity of the signals was determined by the DEPT technique and quoted as follows: (+) for CH_3, CH, (−) for CH_2, and (C_{quat}) for quaternary carbons. IR spectra were recorded on a Bruker IFS 66 (FT-IR) spectrometer. Electron impact (EI) mass spectra were recorded on a Finnigan MAT 95 spectrometer (70 eV); electrospray ionisation (ESI) mass spectra on a Finnigan LCQ spectrometer (70 eV); high-resolution (HR) mass spectra (EI) on a Finnigan MAT-95 spectrometer; HR mass spectra (ESI) on a Bruker APEX-Q 7T IV spectrometer; preselected ion-peak matching at $R \gg 10000$ were within ± 2 ppm of the exact masses. Elemental analyses were measured at the Mikroanalytisches Labor des Instituts für Organische und Biomolekulare Chemie der Universität Göttingen (Germany). Melting points are uncorrected. The solvents used for extraction and chromatography were of technical grade and distilled prior to use. All moisture-sensitive reactions were carried out under dry nitrogen or argon in oven- and/or flame-dried glassware. Column chromatography was carried out on silica gel (Merck; grade 60, 230–400 mesh) and aluminum oxide (ICN Biomedicals; Alumina N, Super I). TLC analysis was carried out on precoated sheets (Macherey-Nagel; 0.25 mm SIL G/UV$_{254}$). Ozonolysis was performed with a Fischer Model 502 instrument. Methyllithium was titrated according to the method of Suffert.[24] Diastereomeric ratios (d.r.) were determined from the ^{13}C NMR spectra of the respective crude products before chromatography or other types of purification methods. THF, diethyl ether, and benzene were distilled from sodium benzophenone ketyl; HMPA and dichloromethane were distilled from CaH_2; acetonitrile was dried over 3-Å molecular sieves.

(*E*)-3-Hydroxy-4-methylhepta-1,4-diene: A solution of vinylmagnesium bromide (240 mL, 0.26 mol, 1.1 M in THF) was added to a stirred solution of (*E*)-2-methyl-2-pentenal[25] (21.7 g, 0.221 mol) in THF (700 mL) over a period of 0.5 h at room temperature. During the addition, the temperature was kept constant by the use of a water bath, and the resulting mixture was stirred for an additional 0.5 h at this temperature. The reaction mixture was quenched by addition of saturated NH_4Cl solution (200 mL) and the resulting organic phase was separated. The aqueous phase was extracted with diethyl ether (3×300 mL) and the combined organic phases were dried over $MgSO_4$. The solvent was evaporated under reduced pressure (20 mbar, 40 °C) to give 26.9 g (96 %) of the title compound as a light-yellow oil. This product was sufficiently pure for the subsequent oxidation, yet could be separated from traces of by-products by Kugelrohr distillation (b.p. 95 °C, 21 mbar), thus yielding 26.1 g (94 %) of the analytically pure alcohol. IR (film): $\tilde{\nu} = 3612$, 2966, 2934, 2875, 1457, 1001, 904, 726, 651 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 0.96$ (t, ^3J(H,H) = 7.4 Hz, 3H, 7-H), 1.62 (s, 3H, CH_3), 1.90 (s_b, 1H, OH), 2.06 (m_c, 2H, 6-H), 4.51 (d, ^3J(H,H) = 5.6 Hz, 1H, 3-H), 5.15 (d, ^3J(H,H) = 11.1 Hz, 1H, 1-H), 5.28 (d, ^3J(H,H) = 18.5 Hz, 1H, 1-H), 5.44 (t, ^3J(H,H) = 6.6 Hz, 1H, 5-H) 5.86 ppm (m_c, 1H, 2-H); ^{13}C NMR (62.9 MHz): $\delta = 11.7$ (+, C7), 13.9 (+, CH_3), 20.8 (−, C6), 78.2 (+, C3), 114.7 (−, C1), 128.6 (+, C5), 135.2 (C_{quat}, C4), 139.3 ppm (+, C2); MS: *m/z* (%): 126 (4) [M^+], 111 (2) [$M^+ - CH_3$], 97 (38) [$M^+ - C_2H_5$], 93 (2), 83 (5), 79 (7), 77 (4), 69 (14) [$C_5H_9^+$], 67 (7), 57 (15) [$M^+ - C_5H_9$], 55 (22), 43 (57), 41 (100); elemental analysis (%) calcd for $C_8H_{14}O$ (126.2): C 76.14, H 11.18; found: C 75.91, H 10.99.

(*E*)-4-Methylhepta-1,4-dien-3-one (11): MnO_2 was successively added in 20-g portions (in total 240 g, 2.76 mol) to a well-stirred solution of (*E*)-3-hydroxy-4-methylhepta-1,4-diene (7.52 g, 59.6 mmol) in benzene (500 mL) every 15 min. After complete addition of the manganese dioxide, the reaction mixture was stirred at room temperature for 2 h. The suspension was filtered through a pad of celite and the residue was washed with diethyl ether (2×500 mL). The combined filtrates were concentrated under reduced pressure (100 mbar, 40 °C) to give 4.54 g of a yellow oil, which was purified by Kugelrohr distillation (b.p. 65 °C, 20 mbar), thus yielding 4.34 g (59 %) of **11** as a yellow oil. IR (film): $\tilde{\nu} =$ 3054, 2973, 1654, 1607, 1410, 1266, 1082, 982, 910, 739, 705 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 1.06$ (t, ^3J(H,H) = 7.3 Hz, 3H, 7-H), 1.80 (s, 3H, CH_3), 2.26 (m_c, 2H, 6-H), 5.66 (dd, ^2J(H,H) = 1.8 Hz, ^3J(H,H) = 10.8 Hz, 1H, 1-H), 6.17 (dd, ^2J(H,H) = 1.8 Hz, ^3J(H,H) = 16.3 Hz, 1H, 1-H), 6.63 (t, ^3J(H,H) = 7.3 Hz, 1H, 5-H), 6.92 ppm (dd, ^3J(H,H) = 10.8, 16.3 Hz, 1H, 2-H); ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta = 11.2$ (+, C7), 12.9 (+, CH_3), 22.3 (−, C6), 127.4 (−, C1), 131.6 (+, C2), 136.8 (C_{quat}, C4), 145.4 (+, C5), 192.0 ppm (C_{quat}, C3); MS: *m/z* (%): 124 (30) [M^+], 123 (6), 109 (55) [$M^+ - CH_3$], 97 (37) [$M^+ - C_2H_3$], 96 (14), 81 (17), 79 (9), 69 (52) [$C_5H_9^+$], 67 (14), 55 (49) [$M^+ - C_5H_9$], 53 (13), 41 (100); elemental analysis (%) calcd for $C_8H_{12}O$ (124.2): C 77.38, H 9.74; found: C 77.24, H 9.73.

3-Ethenyl-1-trimethylsilyloxycyclopent-1-ene (13): A mixture of vinylmagnesium bromide (15.0 mL, 15 mmol, 1.0 M in THF) and HMPA (5.25 mL, 5.41 g, 30.2 mmol) in THF (20 mL) was cooled to −40 °C, copper iodide (230 mg, 1.21 mmol) was added, and the solution was stirred for 20 min. A solution of cyclopent-2-enone (**12**; 820 mg, 9.99 mmol) and chlorotrimethylsilane (3.00 mL, 2.55 g, 23.5 mmol) in THF (10 mL) was added dropwise within 15 min, and the resulting colorless suspension was stirred for 1 h at −40 °C. After the mixture was warmed to room temperature, NEt_3 (3 mL) was added and the reaction mixture was diluted with *n*-heptane (200 mL), washed with water (3× 50 mL), and dried over Na_2SO_4. Concentration under reduced pressure gave 2.16 g of crude product, which after purification by Kugelrohr distillation (40 °C, 0.01 mbar) yielded 1.57 g (86 %) of the silyl enol ether **13** as a colorless oil.[26]

(2*S,3*S**)-3-Ethenyl-2-[(*E*)-4-methyl-3-oxohept-4-enyl]cyclopentanone (23)**: HMPA (780 μL, 803 mg, 4.48 mmol) was added to a stirred solution of silyl enol ether **13** (815 mg, 4.47 mmol) in diethyl ether (24 mL), and the reaction mixture was cooled to 0 °C. After addition of methyllithium (2.29 mL, 4.51 mmol, 1.97 M in Et_2O), the reaction mixture was warmed to room temperature and stirred for 1.5 h. The mixture was then cooled to −78 °C, and a solution of (*E*)-4-methylhepta-1,4-dien-3-one (**11**; 506 mg, 4.07 mmol) in diethyl ether (2 mL) was added within 5 min. After 1.5 h at −78 °C, the reaction was quenched by addition of saturated NH_4Cl solution (10 mL), and the resulting slurry was warmed to room temperature. The aqueous phase was separated and extracted with diethyl ether (2×30 mL). The combined organic phases were dried over $MgSO_4$ and the solvent was removed under reduced pressure (20 mbar, 40 °C), thus yielding 1.38 g of an oil that was purified by column chromatography on silica gel (60 g, hexane/EtOAc 5:1) to give **23** (677 mg; 71 %) as a yellow oil. $R_f = 0.40$; IR (film): $\tilde{\nu} = 2965$, 1734, 1653, 1262, 1097, 909, 807, 734, 651 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 1.07$ (t, ^3J(H,H) = 7.8 Hz, 3H, 7′-H), 1.49–2.02 (m, 4H, 1′(4)-H), 1.75 (s, 3H, CH_3), 2.05–2.48 (m, 6H, 2(5,2′,6′)-H), 2.85 (m_c, 2H, 3(6′)-H), 5.08 (d, ^3J(H,H) = 11.7 Hz, 1H, CH=CH_2), 5.15 (d, ^3J(H,H) = 19.5 Hz, 1H, CH=CH_2), 5.79 (m_c, 1H, CH=CH$_2$), 6.62 ppm (t, ^3J(H,H) = 6.2 Hz, 1H, 5′-H); ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta = 11.1$ (+, C7′), 13.0 (+, CH_3), 22.3 (−, C4), 22.8 (−, C1′), 27.6 (−, C6′), 34.2 (−, C2′), 37.5 (−, C5), 47.3 (+, C3), 53.3 (+, C2), 115.6 (−, CH=CH_2), 136.3 (C_{quat}, C4′), 140.2 (+, CH=CH$_2$), 144.1 (+, C5′), 201.5 (C_{quat}, C3′), 219.7 ppm (C_{quat}, C1); MS: *m/z* (%): 234 (47) [M^+], 205 (28) [$M^+ - C_2H_5$], 165 (6) [$M^+ - C_5H_9$], 149 (11), 137 (6), 123 (6), 112 (22), 109 (15) [$C_7H_9O^+$], 97 (100) [$C_6H_9O^+$], 69 (47) [$C_5H_9^+$], 67 (13), 41 (54); analysis calcd for $C_{15}H_{22}O_2$: 234.1620 (correct mass according to EI-HRMS).

4-Ethenyl-6-ethyl-7-methylspiro[4.5]decane-1,8-dione (9): A stirred solution of **23** (590 mg, 2.52 mmol) in methanol (50 mL) was cooled to 0 °C and finely powdered potassium hydroxide (2.36 g, 42.1 mmol) was added. After all the KOH had dissolved, the cooling bath was removed and the reaction mixture was stirred for 15 h at room temperature. The solution was then poured onto hydrochloric acid (5 %, 11.0 mL) and was extracted with hexane (2×100 mL, 1×50 mL). The combined hexane extracts were washed with saturated $NaHCO_3$ solution (50 mL) and concentrated under reduced pressure (20 mbar, 40 °C) to give 502 mg of crude product. Purification by column chromatography on silica gel (25 g, hexane/EtOAc 5:1) yielded a 72:20:8 mixture (423 mg; 72 %) of three diastereo-

mers (**a**–**c**) of spirocycle **9** as a yellow oil. For spectroscopic analysis, the diastereomers were partially separated by repeated column chromatography on silica gel. Elemental analysis (%) calcd for $C_{15}H_{22}O_2$ (234.3): C 76.88, H 9.46; found: C 77.06, H 9.20. **9a**: $R_f = 0.36$ (hexane/EtOAc 3:1); IR (film): $\tilde{\nu} = 2968, 2936, 2878, 1727, 1709, 1457, 1379, 910, 733, 649\ cm^{-1}$; ^1H NMR (250 MHz, $CDCl_3$): $\delta = 0.87$–1.01 (m, 6H, CH_2CH_3, CH_3), 1.08–1.53 (m, 3H, 3-H, CH_2CH_3), 1.61–1.94 (m, 4H, 3(9,10)-H), 2.01–2.62 (m, 4H, 2(6,7)-H), 2.85 (m_c, 1H, 4-H), 2.93 (m_c, 1H, 10-H), 5.07 (m_c, 2H, $CH{=}CH_2$), 5.77 ppm (m_c, 1H, $CH{=}CH_2$); ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta = 12.2$ (+, CH_2CH_3), 15.9 (+, CH_3), 19.9 (−, CH_2CH_3), 25.0 (−, C10), 26.7 (−, C3), 35.9 (−, C2), 37.1 (−, C9), 44.1 (+, C6), 47.6 (+, C4), 48.3 (+, C7), 54.9 (C_{quat}, C5), 116.1 (−, $CH{=}CH_2$), 137.8 (+, $CH{=}CH_2$), 213.6 (C_{quat}, C8), 221.2 ppm (C_{quat}, C1); MS: *m/z* (%): 234 (92) [M^+], 205 (100) [$M^+ - C_2H_5$], 164 (25), 159 (41), 137 (17), 136 (24), 122 (18), 112 (25), 109 (20) [$C_7H_9O^+$], 97 (25) [$C_6H_9O^+$], 78 (32), 67 (21), 55 (21), 41 (44). **9b**: $R_f = 0.31$ (hexane/EtOAc 3:1); IR (film): $\tilde{\nu} = 2970, 1728, 1708, 1456, 1380, 909, 734, 650\ cm^{-1}$; ^1H NMR (250 MHz, $CDCl_3$): $\delta = 0.88$ (t, $^3J(H,H) = 7.4$ Hz, 3H, CH_2CH_3), 1.01 (d, $^3J(H,H) = 7.4$ Hz, 3H, CH_3), 1.20–1.58 (m, 3H, 3-H, CH_2CH_3), 1.62–1.96 (m, 4H, 3(9,10)-H), 2.02–2.65 (m, 4H, 2-(6,7)-H), 2.95 (m_c, 1H, 4-H), 3.27 (m_c, 1H, 10-H), 5.12 (m_c, 2H, $CH{=}CH_2$), 5.76 ppm (m_c, 1H, $CH{=}CH_2$); ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta = 12.6$ (+, CH_2CH_3), 14.1 (+, CH_3), 24.1 (−, CH_2CH_3), 24.5 (−, C10), 26.2 (−, C3), 36.1 (−, C2), 38.2 (−, C9), 46.0 (+, C6), 47.5 (+, C4), 48.9 (+, C7), 54.7 (C_{quat}, C5), 117.8 (−, $CH{=}CH_2$), 135.7 (+, $CH{=}CH_2$), 212.8 (C_{quat}, C8), 220.8 ppm (C_{quat}, C1); MS: *m/z* (%): 234 (40) [M^+], 205 (49) [$M^+ - C_2H_5$], 165 (21) [$M^+ - C_5H_9$], 164 (100), 136 (49), 123 (18), 112 (27), 109 (30) [$C_7H_9O^+$], 97 (30) [$C_6H_9O^+$], 93 (17), 79 (37), 69 (17) [$C_5H_9^+$], 55 (25), 41 (49). **9c**: $R_f = 0.28$ (hexane/EtOAc 3:1); IR (film): $\tilde{\nu} = 2970, 1734, 1710, 1464, 1380, 909, 734, 650\ cm^{-1}$; ^1H NMR (250 MHz, $CDCl_3$): $\delta = 0.81$ (t, $^3J(H,H) = 7.4$ Hz, 3H, CH_2CH_3), 1.03 (d, $^3J(H,H) = 7.4$ Hz, 3H, CH_3), 1.12–1.33 (m, 2H, CH_2CH_3), 1.35–1.64 (m, 2H, 3-H), 1.67–2.12 (m, 4H, 9(10)-H), 2.15–2.55 (m, 4H, 2(6,7)-H), 3.09 (m_c, 1H, 4-H), 5.12 (d, $^3J(H,H) = 9.2$ Hz, 1H, $CH{=}CH_2$), 5.23 (d, $^3J(H,H) = 16.5$ Hz, 1H, $CH{=}CH_2$), 6.06 ppm (m_c, 1H, $CH{=}CH_2$); ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta = 12.5$ (+, CH_2CH_3), 14.4(+, CH_3), 24.1 (−, CH_2CH_3), 25.2 (−, C10), 27.2 (−, C3), 36.7 (−, C2), 36.9 (−, C9), 45.3 (+, C6), 46.1 (+, C4), 47.7 (+, C7), 55.2 (C_{quat}, C5), 117.1 (−, $CH{=}CH_2$), 138.9 (+, $CH{=}CH_2$), 212.3 (C_{quat}, C8), 221.0 ppm (C_{quat}, C1); MS: *m/z* (%): 234 (6) [M^+], 205 (7) [$M^+ - C_2H_5$], 165 (14) [$M^+ - C_5H_9$], 164 (100), 149 (17), 136 (57), 122 (22), 109 (17) [$C_7H_9O^+$], 97 (7) [$C_6H_9O^+$], 79 (25), 69 (7) [$C_5H_9^+$], 57 (10), 41 (29).

4-Ethenyl-6-ethyl-7-methylspiro[4.5]dec-6-ene-1,8-dione (25): Pyridine (314 μL, 3.90 mmol) and chlorotrimethylsilane (491 μL, 3.84 mmol) were successively added to the 72:20:8 mixture of the diastereomeric spirocycles **9a**/**9b**/**9c** (758 mg, 3.23 mmol), and the reaction mixture was warmed to 60 °C. Then, a solution of sodium iodide (582 mg, 3.88 mmol) in acetonitrile (3.90 mL) was added, and the reaction mixture was stirred at 60 °C for 1 h. The resulting brown solution was poured onto an ice-cooled mixture of pentane (20 mL) and water (6 mL). After separation of the phases, the aqueous phase was extracted with pentane (2×12 mL), and the combined organic phases were dried over $MgSO_4$. Removal of the solvent under reduced pressure (20 mbar, 40 °C) gave 888 mg of the crude silyl enol ethers as a clear oil, which was directly dissolved in benzene (8 mL). After addition of *para*-toluenesulfonic acid (TsOH; 11.0 mg, 57.8 μmol), the reaction mixture was heated to reflux for 2 h and then cooled to room temperature. A solution of collidine (776 μL, 5.87 mmol) in benzene (6 mL) was added to a stirred solution of DDQ (1.27 g, 5.59 mmol) in benzene (25 mL) within 10 min at room temperature. The aforementioned solution containing the crude silyl enol ether **24** in benzene was added within 10 min, and the reaction mixture was stirred at room temperature for 1.5 h. The solution was diluted with diethyl ether (90 mL) and washed with aqueous NaOH solution (1.0 M, 2× 36 mL). The separated aqueous phase was extracted with diethyl ether (90 mL), and the combined organic phases were washed with hydrochloric acid (1.0 M, 90 mL) and saturated $NaHCO_3$ solution (90 mL) and dried over $MgSO_4$. Evaporation of the solvent under reduced pressure gave 704 mg of crude product, which was purified by column chromatography on silica gel (50 g, hexane/EtOAc 5:1), thus yielding 434 mg (58%) of a 90:10 mixture of (4*S**,5*R**)-**25** and (4*S**,5*S**)-**25** as a clear oil. Separation of the diastereomers was accomplished by repeated column chromatography on silica gel, thus giving 372 mg (50%) of (4*S**,5*R**)-**25** and 31.1 mg (4%) of (4*S**,5*S**)-**25**. Elemental analysis (%) calcd for $C_{15}H_{20}O_2$ (232.3): C 77.55, H 8.68; found: C 77.17 H 8.68. (4*S**,5*R**)-**25**: $R_f = 0.23$ (hexane/EtOAc 3:1); IR (film): $\tilde{\nu} = 2933, 1734, 1700, 1663, 1457, 1380, 908, 734, 650\ cm^{-1}$; ^1H NMR (250 MHz, $CDCl_3$): $\delta = 1.06$ (t, $^3J(H,H) = 7.9$ Hz, 3H, CH_2CH_3), 1.65–2.11 (m, 6H, 3(10)-H, CH_2CH_3), 1.87 (s, 3H, CH_3), 2.14–2.65 (m, 4H, 2(9)-H), 3.23 (m_c, 1H, 4-H), 5.11–5.23 (m, 2H, $CH{=}CH_2$), 5.87 ppm (m_c, 1H, $CH{=}CH_2$); ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta = 11.8$ (+, CH_2CH_3), 12.7 (+, CH_3), 23.6 (−, CH_2CH_3), 24.2 (−, C10), 25.4 (−, C3), 32.9 (−, C2), 37.2 (−, C9), 47.2 (+, C4), 59.0 (C_{quat}, C5), 117.2 (−, $CH{=}CH_2$), 136.0 (+, $CH{=}CH_2$), 136.1 (C_{quat}, C7), 156.1 (C_{quat}, C6), 198.2 (C_{quat}, C8), 217.1 ppm (C_{quat}, C1); MS: *m/z* (%): 232 (92) [M^+], 214 (39), 204 (22), 203 (63) [$M^+ - C_2H_5$], 190 (12), 178 (100), 176 (50) [$M^+ - C_2H_5 - C_2H_3$], 161 (45), 147 (61), 133 (49), 119 (70), 105 (67), 91 (92), 79 (53), 67 (45), 53 (39), 41 (78). (4*S**,5*S**)-**25**: $R_f = 0.23$ (hexane/EtOAc 3:1); IR (film): $\tilde{\nu} = 2930, 1737, 1709, 1670, 1453, 1377, 910, 733, 649\ cm^{-1}$; ^1H NMR (250 MHz, $CDCl_3$): $\delta = 1.06$ (t, $^3J(H,H) = 7.9$ Hz, 3H, CH_2CH_3), 1.63–2.10 (m, 6H, 3(10)-H, CH_2CH_3), 1.80 (s, 3H, CH_3), 2.14–2.65 (m, 4H, 2(9)-H), 3.06 (m_c, 1H, 4-H), 4.95–5.09 (m, 2H, $CH{=}CH_2$), 5.66 ppm (m_c, 1H, $CH{=}CH_2$); ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta = 11.0$ (+, CH_2CH_3), 12.2 (+, CH_3), 27.1 (−, CH_2CH_3), 27.9 (−, C10), 32.6 (−, C3), 34.2 (−, C2), 37.9 (−, C9), 51.8 (+, C4), 58.5 (C_{quat}, C5), 116.5 (−, $CH{=}CH_2$), 135.4 (+, $CH{=}CH_2$), 138.6 (C_{quat}, C7), 157.5 (C_{quat}, C6), 197.7 (C_{quat}, C8), 219.9 ppm (C_{quat}, C1); MS: *m/z* (%): 232 (95) [M^+], 214 (41), 203 (69) [$M^+ - C_2H_5$], 189 (14), 178 (100), 176 (50) [$M^+ - C_2H_5 - C_2H_3$], 161 (48), 147 (67), 133 (49), 119 (68), 105 (64), 91 (94), 79 (55), 67 (40), 55 (26), 41 (75).

(4*S,5*R**)-4-Ethenyl-6-ethyl-7-methyl-8-trimethylsilyloxyspiro[4.5]deca-6,8-diene-1-one (26)**: A solution of the (4*S**,5*R**)-diastereomer of spirocycle **25** (372 mg, 1.60 mmol) in dichloromethane (15 mL) was cooled to −78 °C. At this temperature, NEt_3 (686 μL, 4.92 mmol) and TMSOTf (325 μL, 1.80 mmol) were successively added and the solution was then stirred for 0.5 h. The reaction mixture was diluted with pentane (50 mL) and washed with water (2×10 mL). Drying over $MgSO_4$ and removal of the solvent under reduced pressure yielded 458 mg (94%) of silyl enol ether **26** as a colorless oil which slowly started to crystallize. This material was pure enough to be used in the next step. An analytical sample was obtained by column chromatography on aluminum oxide (25 g, hexane/EtOAc 3:1). $R_f = 0.76$; IR (film): $\tilde{\nu} = 2967, 1734, 1653, 1457, 1353, 1253, 1207, 1103, 908, 873, 846, 733, 651\ cm^{-1}$; ^1H NMR (250 MHz, $CDCl_3$): $\delta = 0.17$ (s, 9H, $Si(CH_3)_3$), 1.02 (t, $^3J(H,H) = 7.8$ Hz, 3H, CH_2CH_3), 1.71 (s, 3H, CH_3), 1.77–1.98 (m, 4H, 3(10)-H), 2.02–2.15 (m, 2H, CH_2CH_3), 2.22–2.45 (m, 2H, 2-H), 2.68 (m_c, 1H, 4-H), 4.51 (dd, $^3J(H,H) = 4.0$, 6.2 Hz, 1H, 9-H), 4.88 (d, $^3J(H,H) = 11.7$ Hz, 1H, $CH{=}CH_2$), 4.96 (d, $^3J(H,H) = 17.6$ Hz, 1H, $CH{=}CH_2$), 5.96 ppm (m_c, 1H, $CH{=}CH_2$); ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta = 0.2$ (+, $Si(CH_3)_3$), 12.5 (+, CH_2CH_3), 13.6 (+, CH_3), 23.2 (−, C10), 24.5 (−, C3), 26.9 (−, CH_2CH_3), 38.6 (−, C2), 49.8 (+, C4), 59.2 (C_{quat}, C5), 97.6 (+, C9), 113.6 (−, $CH{=}CH_2$), 130.3 (C_{quat}, C6), 135.4 (C_{quat}, C7), 137.6 (+, $CH{=}CH_2$), 149.1 (C_{quat}, C8), 223.6 ppm (C_{quat}, C1); MS: *m/z* (%): 304 (16) [M^+], 289 (5) [$M^+ - CH_3$], 275 (6) [$M^+ - C_2H_5$], 263 (9), 247 (41), 235 (100), 219 (21), 209 (67), 193 (35), 96 (5), 73 (47) [TMS^+], 68 (13); analysis calcd for $C_{18}H_{28}O_2Si$: 305.19313 [$M+H$]$^+$ (correct mass according to ESI-HRMS).

4-Ethenyl-6-ethyl-7,9-dimethylspiro[4.5]dec-6-ene-1,8-dione (27): Silver trifluoroacetate (68.5 mg, 0.310 mmol) was suspended in dichloromethane (1 mL) and the resulting slurry was cooled to 0 °C. At this temperature, a solution of silyl enol ether **26** (86.0 mg, 0.282 mmol) in dichloromethane (1 mL) and iodomethane (43.0 μL, 0.691 mmol) were added successively and the reaction mixture was stirred for 2 h at room temperature. The mixture was filtered through a pad of celite and washed with diethyl ether (10 mL). Removal of the solvent under reduced pressure furnished 77.9 mg of a yellow oil, which was purified by column chromatography on silica gel (10 g, hexane/EtOAc 5:1) to yield 24.3 mg (37%) of **25** and 43.1 mg (62%) of a 86:14 mixture of (4*S**,5*R**,9*S**)-**27** and (4*S**,5*R**,9*R**)-**27** as a clear oil. Slow crystallization of this oil occurred on cooling to −18 °C. $R_f = 0.38$ (hexane/EtOAc 3:1); m.p. 62 °C; IR (film): $\tilde{\nu} = 2933, 1734, 1663, 1457, 1380, 908, 734, 650\ cm^{-1}$; ^1H NMR (250 MHz, $CDCl_3$, signals of the minor isomer are marked with "*"): $\delta = 1.03/1.06$* (d, $^3J(H,H) = 7.1$ Hz, 3H, CH_3), 1.08*/1.18 (t, $^3J(H,H) = 7.2$ Hz,

3H, CH_2CH_3), 1.51–2.08 (m, 4H, 3(10)-H), 1.83/1.85* (s, 3H, CH_3), 2.10–2.43 (m, 3H, 2-H, CH_2CH_3), 2.45–2.70 (m, 2H, 2(9)-H), 3.07/3.30* (m_c, 1H, 4-H), 5.07–5.27 (m, 2H, CH=CH_2), 5.78*/5.97 ppm (m_c, 1H, CH=CH_2); ^{13}C NMR (62.9 MHz, $CDCl_3$, signals of the minor isomer are marked with "*"): δ = 11.9*/12.1 (+, CH_2CH_3), 12.6*/13.2 (+, CH_3), 15.4*/15.6 (+, CH_3), 24.7 (−, CH_2CH_3), 26.1*/26.2 (−, C10), 33.5/33.5* (−, C3), 36.6 (−, C2), 38.1 (+, C9), 48.5*/48.6 (+, C4), 60.3/60.3* (C_{quat}, C5), 116.6*/116.8 (−, CH=CH_2), 135.6*/135.7 (+, CH=CH_2), 136.5 (C_{quat}, C7), 155.3*/155.3 (C_{quat}, C6), 200.2/200.6* (C_{quat}, C8), 220.0*/220.0 ppm (C_{quat}, C1); MS: *m/z* (%): 246 (45) [M^+], 217 (21) [$M^+ - C_2H_5$], 204 (74), 192 (45), 178 (100), 150 (36), 136 (21), 119 (14), 107 (13), 91 (25), 79 (20), 41 (28); elemental analysis (%) calcd for $C_{16}H_{22}O_2$ (246.3): C 78.01, H 9.00; found: C 77.72, H 8.85.

(1*R,5*R**,9*S**)-6-Ethyl-7,9-dimethyl-4,8-dioxospiro[4.5]dec-6-ene-1-carboxylic acid (1)**: Pyridine (227 μL, 2.81 mmol) was added to a solution of the 86:14 mixture of (4*S**,5*R**,9*S**)-**27** and (4*S**,5*R**,9*R**)-**27** (356 mg, 1.45 mmol) in dichloromethane (28 mL) and the reaction mixture was cooled to −55 °C. Ozonized oxygen was passed discontinuously through the solution at a rate of 20 L h^{-1} until analysis by TLC indicated complete consumption of the starting material (2 min). The reaction mixture was warmed to room temperature, formic acid (97%, 2.00 mL, 51.4 mmol) and aqueous hydrogen peroxide (30%, 0.96 mL, 9.40 mmol) were added, and the reaction mixture was stirred for 19 h. The reaction mixture was washed with hydrochloric acid (1.0 M, 50 mL), the aqueous phase was extracted with ethyl acetate (3 × 100 mL), and the combined organic phases were dried over $MgSO_4$. Removal of the solvent under reduced pressure gave 450 mg of a yellow oil, which was purified by column chromatography on silica gel (25 g, $CHCl_3$/MeOH 95:5) to furnish a colorless solid (R_f = 0.24). Final recrystallization from hexane/acetone yielded 215 mg (56%) of **1**. The physical and spectroscopic data were consistent with the data of spirodionic acid isolated from *Streptomyces* sp.[1]. Elemental analysis (%) calcd for $C_{15}H_{20}O_4$ (264.3): C 68.16, H 7.63; found: C 67.95 H 7.65.

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