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Synthesis of butenolides recently isolated from marine microorganisms

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Abstract—The syntheses and ^{13}C NMR analyses of four diastereomeric butenolides, two of which were recently isolated from the marine microorganisms *Streptomycete* B 5632 and *Streptoverticillium luteoverticillatum* 11014 are described. The two isolated butenolides were found to be one of the two diastereomers (4*S*,10*R**,11*R**)-4,11-dihydroxy-10-methyl-dodec-2-en-1,4-olide (***RRS*-1** or ***SSS*-1**) and one of the two diastereomers (4*S*,10*S**,11*R**)-4,11-dihydroxy-10-methyl-dodec-2-en-1,4-olide (***SRS*-1** or ***RSS*-1**). An asymmetric 1,3-dipolar cycloaddition of a thiocarbonyl ylide with a dipolarophile attached to camphorsultam and a ring-opening of an enantiomerically pure vinyloxirane by lithiated dithiane served as key steps for the construction of the three stereogenic centres. Further elaborations including ring-closing metathesis and Mitsunobu inversion furnished the four diastereomeric butenolides.

Butenolides, a class of α,β-unsaturated lactones, are substances produced by organisms such as bacteria, fungi and gorgonians.[1] In *Streptomyces* some saturated analogues function as signal substances, for example, to cause synchronised morphological differentiation, such as aerial mycelium and spore formation or physiological differentiation leading to production of secondary metabolites.[2] Some butenolides show inhibitor activities[3] and antifeedant properties.[4]

Recently, two new butenolides were isolated from the marine *Streptomycete* B 5632[5a] and *Streptoverticillium luteoverticillatum* 11014,[5b] and characterised by ^{13}C NMR analysis as a mixture of two diastereomers of **1** (Fig. 1). This diastereomeric mixture has shown cytotoxic activity in human leukaemia K562 and murine lymphoma P388 cell lines.[5b] The absolute configuration at C-4 has been assigned *S* via CD-measurements.[5a]

As no syntheses of these compounds have been reported and since only one out of the three stereogenic centres of butenolide **1** was determined, we decided to synthesise all four diastereomers of **1** in enantiomerically pure form, all having *S*-configuration at C-4. From ^{1}H and ^{13}C NMR data for these four diastereomers we should be able to determine the absolute configurations of the two remaining stereogenic centres of the natural diastereomeric butenolides.

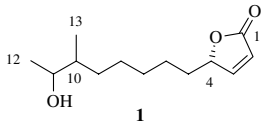

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Figure 1. Two diastereomeric butenolides isolated from a marine *Streptomycete* B 5632 and *Streptoverticillium luteoverticillatum* 11014 with *S*-configuration at C-4.

Target molecule **1** incorporates a 3-methyl-2-alkanol unit, which is a common structural moiety present in several natural products.[6] We have recently demonstrated that the *R***S**-isomer of this unit can be prepared efficiently in enantiomerically pure form via an asymmetric 1,3-dipolar cycloaddition of a thiocarbonyl ylide with a benzyloxy substituted dipolarophile attached to camphorsultam.[7] Using such a reaction and two sequential alkylations of dithiane as key steps, we prepared the active sex pheromone component of *Macrodiprion nemoralis*.[8] The final step in that sequence was simultaneous removal of a benzyl group and reduction of a dithiane and a tetrahydrothiophene unit through treatment with Raney-Nickel. Keeping in mind that butenolides **1** incorporate a double bond and thus, should be

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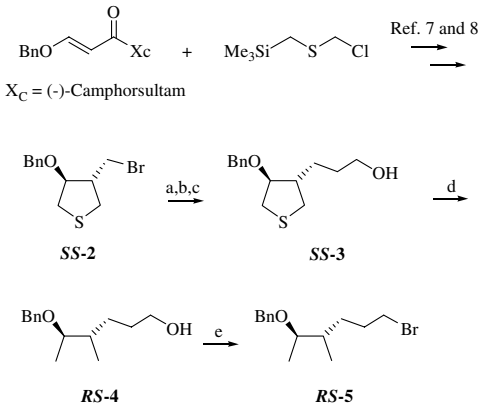
sensitive to this reagent, we envisaged that a similar strategy, but with some modifications, could be used for the preparation of R^*S^*S-isomers of **1**. A Mitsunobu reaction would then furnish the S^*S^*S-isomers of **1**.

In the synthesis of natural products containing a butenolide unit, various methods exist for the construction of this moiety.[9] Due to its simplicity, ring-closing metathesis has emerged as the most popular.[10] Using such a strategy, the diene depicted in Scheme 1 could serve as a precursor to the ***R**S*S*-1** isomers. To create the C-4 stereogenic centre in **1,** vinyloxirane (commercially available in both enantiomeric forms) could serve as a building block in our synthetic sequence. Thus, two sequential alkylations of dithiane with vinyloxirane and a protected 3-methyl-2-alkylhalide-2-ol chiral building block (Scheme 1) followed by further transformations would result in a carbon chain containing all of the three stereogenic centres of butenolide **1**. As mentioned above, the enantiomerically pure 3-methyl-2-alkanol units were obtained via an asymmetric 1,3-dipolar cycloaddition, followed by a two carbon chain elongation (Scheme 1).

As a representative example, we describe in detail the total synthesis of ***RSS***- and ***SSS*-1**, which commenced with the construction of the chiral building block ***RS*-5** (Scheme 2). Bromide ***RS*-5** was obtained via a five-step sequence from enantiomerically pure ***SS*-2**,[7,8] in a good overall yield (Scheme 2). As have been reported by us previously for a similar compound,[8] it was important to perform the Raney-Nickel reduction (***SS*-3→*RS*-4**) in acetone, since in other solvents (alcohols, acetic acid, toluene and THF) cleavage of the Bn–O bond also occurred.

Bromide ***RS*-5** was then coupled with monoalkylated dithiane ***S*-6**, obtained from ring-opening of (*R*)-vinyloxirane with lithiated dithiane (Scheme 3). This furnished disubstituted dithiane ***RSS*-7** in 81% yield.

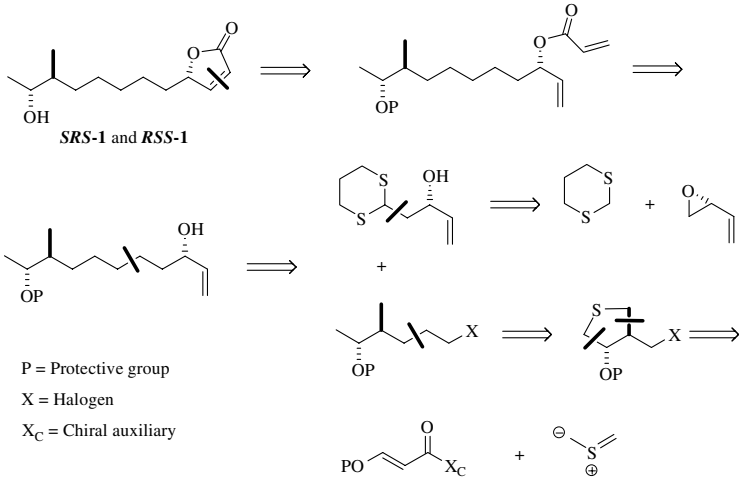
Our strategy was then to esterify ***RSS*-7** with acryloyl chloride followed by a ring-closing metathesis of the resulting diene using either Grubbs catalyst **I** or **II**.



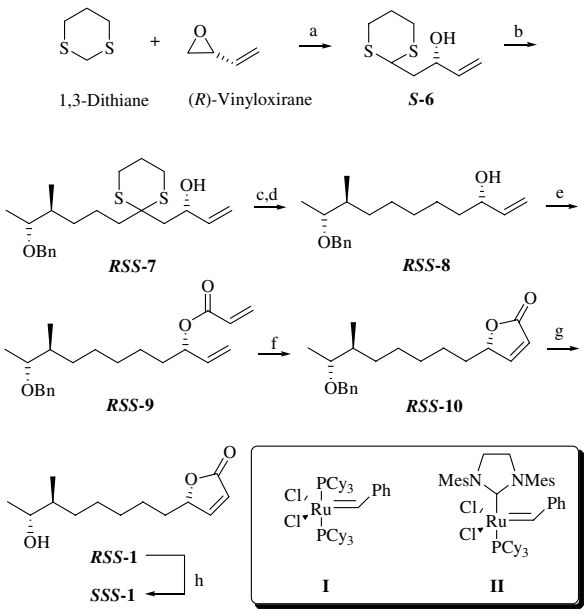
Scheme 2. Synthesis of chiral building block ***RS*-5**. Reagents and conditions: (a) (i) dimethyl malonate, NaH, THF, reflux; (ii) 0.1 M HCl (aq); (b) NaCl, DMSO/H_2O 94:6, 170 °C; (c) (i) $LiAlH_4$, THF, 0 °C; (ii) 0.1 M HCl (aq), 71% yield from ***SS*-2**; (d) W-2 Raney-Nickel, H_2, acetone, room temperature, 5 d, 68% yield; (e) $P(Ph)_3$, Br_2, imidazole, CH_2Cl_2, 91% yield.

However, all attempts failed in the ring-closing step and only the starting material was recovered. Many other researchers have also reported difficulties in ring-closing when the diene substrate incorporates sulfur atoms.[11] Thus, the dithiane unit was removed before the ring-closing-step in a three-step sequence as outlined in Scheme 3. Dithiane ***RSS*-7** was transformed to the corresponding ketone using a method reported by Stork and Zhao[12] followed by condensation with *p*-tosylhydrazide to a *p*-tosylhydrazone intermediate, which was immediately reduced with catecholborane to compound ***RSS*-8** in 72% yield. We also attempted to reduce the intermediate ketone under Huang–Minlon conditions. However, only reduced retro-aldol products were obtained.

Next we esterified alcohol ***RSS*-8** by treatment with acryloyl chloride and a base to give ester ***RSS*-9**. It was found that when using amine bases (Et_3N, DMAP and pyridine) in various solvents, low yields of ester ***RSS*-9** were obtained. However, deprotonation of ***RSS*-8** with *n*-BuLi in THF followed by addition of



Scheme 1. Retrosynthetic analysis of the diastereomeric butenolides ***SRS*-1** and ***RSS*-1**.



Scheme 3. Reagents and conditions: (a) (i) 1,3-dithiane, *n*-BuLi, THF, −20 °C, 1 h; (ii) −78 °C, (*R*)-vinyloxirane (0.70 equiv); (iii) NH_4Cl (aq satd), 72% yield; (b) (i) *n*-BuLi, THF, −20 °C, 4 h; (ii) add ***RS*-5**, −20 °C→room temperature; (iii) NH_4Cl (aq satd), 81% yield; (c) Bis[trifluoroacetoxy]iodobenzene, MeOH/H_2O 9:1, 72% yield; (d) (i) *p*-toluenesulfonohydrazide, EtOH, 24 h; (ii) Catecholborane, THF, 0 °C; (iii) $NaOAc{\cdot}3H_2O$, reflux, 1 h, 81% yield; (e) (i) *n*-BuLi, THF, 5 min; (ii) acryloyl chloride, 84% yield; (f) Grubbs catalyst **II**, 5 mol %, CH_2Cl_2, reflux, 1 h, 86% yield; (g) (i) BCl_3 (1 M in hexane, 2 equiv), CH_2Cl_2, −78 °C; (ii) MeOH at −78 °C, 48% yield; (h) (i) PPh_3, 3,5-dinitrobenzoic acid, DEAD, THF, 0 °C→room temperature; (ii) MeOH/THF 1:1, 1 M K_2CO_3 (aq), 0 °C, 5% yield.

acryloyl chloride resulted in a good yield of ester ***RSS*-9**. Diene ***RSS*-9** was then subjected to Grubbs catalyst **II**[13] (5 mol %) to give butenolide ***RSS*-10** in full conversion within 1 h. It was obvious that catalyst **II** was superior in comparison with catalyst **I**[13] as low conversions were obtained using the latter as catalyst also under prolonged reaction times. It is known that dienes, where one of the double bonds is conjugated to a carbonyl, often display low reactivity in the presence of catalyst **I**, due to coordination of the catalyst to the carbonyl of the α,β-unsaturated moiety.[14] Although this coordination to ruthenium can be circumvented by the addition of a Lewis acid such as $Ti(OEt)_4$,[14] we found it more convenient to use catalyst **II**. Finally, removal of the benzyl group of ***RSS*-10** was accomplished by treatment with BCl_3[15] to give ***RSS*-1** isomer.[16] ***SSS*-1** isomer was obtained through inversion of the configuration at C-11 using the Mitsunobu reaction,[17] followed by hydrolysis of the intermediate ester.[17] Butenolide ***SSS*-1**[18] was obtained in poor yield, as along with the desired product, a saturated straight chain γ-keto methyl ester (according to ^1H NMR) was also isolated from the hydrolysis. Most probably, this was formed due to isomerisation of the double bond and transesterification of the butenolide with the solvent (MeOH) followed by tautomerisation of the enol to the keto form. This γ-keto methyl ester was also isolated as a by-product in the above described removal of the protective benzyl group with BCl_3 in compound ***RSS*-10**. Butenolides ***SRS*-**[19] and ***RRS*-1**[20] were prepared as above (see Scheme 2) but using the other enantiomer of camphorsultam as chiral auxiliary.

The ^{13}C NMR data of the isolated natural butenolides were assigned as a 1:1 diastereomeric mixture but the assignment of the carbons made in the literature was ambiguous.[5] When comparing the published ^{13}C NMR data with our data for the synthetic compounds ***RRS*-1**, ***SSS*-1**, ***SRS*-1** and ***RSS*-1** it was confirmed that the resonances listed in the literature for each of the diastereomers were a mixture of both isomers (see Table 1). Our data show that the two naturally occurring diastereomers are those with ***R***R***S*-** and ***S***R***S*-** configuration.

In conclusion, we have accomplished the total syntheses of enantiomerically pure diastereomeric butenolides **1**, recently isolated from marine *Streptomycete* B 5632 and *S. luteoverticillatum* 11014, via a seven-step sequence. According to our ^{13}C NMR analyses the two diastereomers previously isolated from natural sources by two other research groups as a 1:1 mixture consists of one of the two diastereomers (4*S*,10*R**,11*R**)-4,11-dihydroxy-10-methyl-dodec-2-en-1,4-olide (***RRS*-1** or ***SSS*-1**)

Table 1. ^{13}C NMR (125 MHz, $CDCl_3$) data for the synthetically prepared butenolides in comparison with the isolated butenolide mixture

	Atom	***RSS*-1**	***SSS*-1**	***SRS*-1**	***RRS*-1**	Ref. 5a[a]		Ref. 5b[b]	
1	CO	173.19	173.17	173.19	173.15	173.2	173.2	173.2	173.2
2	CH	121.55	121.58	121.54	121.57	121.6	121.6	121.5	121.5
3	CH	156.30	156.26	156.30	156.23	156.3	156.3	156.3	156.3
4	CH	83.41	83.39	83.41	83.38	83.4	83.4	83.4	83.4
5	CH_2	33.16	33.17	33.15	33.16	32.4	33.2	33.1	33.1
6	CH_2	24.97	24.97	24.95	24.97	25.0	25.0	24.9	24.9
7	CH_2	29.60	29.61	29.60	29.60	29.6	29.7	29.6	29.6
8	CH_2	26.99	27.13	26.98	27.12	27.0 (*R**S**S*)[c]	27.1 (*R**R**S*)[c]	27.0 (*R**S**S*)[c]	27.1 (*R**R**S*)[c]
9	CH_2	32.35	32.42	32.34	32.42	32.4	32.4	32.4	32.4
10	CH	39.99	39.69	39.97	39.67	39.6 (*R**R**S*)[c]	40.0 (*R**S**S*)[c]	39.6 (*R**R**S*)[c]	39.9 (*R**S**S*)[c]
11	CH	71.72	71.33	71.70	71.31	71.3 (*R**R**S*)[c]	71.7 (*R**S**S*)[c]	71.3 (*R**R**S*)[c]	71.7 (*R**S**S*)[c]
12	CH_3	19.51	20.27	19.49	20.26	19.5 (*R**S**S*)[c]	20.3 (*R**R**S*)[c]	19.4 (*R**S**S*)[c]	20.2 (*R**R**S*)[c]
13	CH_3	14.58	14.15	14.57	14.11	14.2 (*R**R**S*)[c]	14.6 (*R**S**S*)[c]	14.2 (*R**R**S*)[c]	14.5 (*R**S**S*)[c]

[a] A mixture of two diastereomers in a ratio close to 1:1 ($CDCl_3$, 75 or 125 MHz).
[b] A mixture of two diastereomers with unknown composition ($CDCl_3$, 150 MHz).
[c] Assigned configurations based on our ^{13}C NMR data.

and one of the two diastereomers (4*S*,10*S**, 11*R**)-4,11-dihydroxy-10-methyl-dodec-2-en-1,4-olide (***SRS*-1** or ***RSS*-1**).

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Supplementary data

Experimental procedures, analytical data and NMR spectra concerning the total synthesis of ***RSS*-1**, and analytical data and NMR spectra for ***SSS*-**, ***SRS*-** and ***RRS*-1** are given. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.08.123.

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16. Data for ***RSS*-1**: >99% (GC). $[\alpha]_D^{20}$ +42.9 (*c* 0.359, MeOH), ^{1}H NMR (500 MHz, $CDCl_3$, Me_4Si): δ 0.86 (3H, d, $J = 6.7$ Hz), 1.05–1.11 (m, 1H), 1.13 (3H, d, $J = 6.4$ Hz), 1.20–1.52 (9H, m), 1.63–1.70 (1H, m), 1.74–1.81 (1H, m), 3.65 (1H, quintet, $J \sim 6.1$ Hz), 5.03–5.06 (1H, m), 6.11 (1H, dd, $J = 5.7$, 2.0 Hz), 7.46 (1H, dd, $J = 5.7$, 1.4 Hz). ^{13}C NMR (125 MHz, $CDCl_3$, Me_4Si): see Table 1. MS (EI) *m*/*z* (relative intensity): 227 (MH^+, 20%), 209 (MH^+-H_2O, 53), 191 (9), 182 (5), 164 (8), 149 (9), 135 (8), 122 (100), 107 (18), 97 (60), 81 (21), 67 (23), 55 (40), 45 (29). LC–HRMS: Found (M^+-H, $C_{13}H_{21}O_3$) 225.1490, calcd (M^+-H, $C_{13}H_{21}O_3$) 225.1496.
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18. Data for ***SSS*-1**: 87% (GC). ^{1}H NMR (500 MHz, $CDCl_3$, Me_4Si): δ 0.88 (3H, d, $J = 6.7$ Hz), 1.09–1.16 (1H, m), 1.15 (3H, d, $J = 6.3$ Hz), 1.24–1.53 (9H, m), 1.64–1.71 (1H, m), 1.74–1.79 (1H, m), 3.69–3.73 (1H, m), 5.03–5.06 (1H, m), 6.11 (1H, dd, $J = 5.7$, 1.9 Hz), 7.45 (1H, dd, $J = 5.7$, 1.3 Hz). ^{13}C NMR (125 MHz, $CDCl_3$, Me_4Si): see Table 1. MS (EI) *m*/*z* (relative intensity): 227 (MH^+, 4%), 209 (MH^+-H_2O, 33), 191 (6), 182 (7), 164 (8), 149 (7), 135 (9), 122 (100), 107 (17), 97 (83), 81 (27), 67 (30), 55 (48), 45 (32). LC–HRMS: Found (M^+-H, $C_{13}H_{21}O_3$) 225.1502, calcd (M^+-H, $C_{13}H_{21}O_3$) 225.1496.
19. Data for ***SRS*-1**: >99% (GC). $[\alpha]_D^{20}$ +70.9 (*c* 0.115, MeOH), ^{1}H NMR (500 MHz, $CDCl_3$, Me_4Si): δ 0.87 (3H, d, $J = 6.7$ Hz), 1.06–1.16 (1H, m), 1.13 (3H, d, $J = 6.3$ Hz), 1.21–1.53 (9H, m), 1.63–1.70 (1H, m), 1.74–1.81 (1H, m), 3.65 (1H, quintet, $J \sim 6.1$ Hz), 5.03–5.06 (1H, m), 6.11 (1H, dd, $J = 5.7$, 2.0 Hz), 7.46 (1H, dd, $J = 5.7$, 1.4 Hz). ^{13}C NMR (125 MHz, $CDCl_3$, Me_4Si): see Table 1. MS (EI) *m*/*z* (relative intensity): 227 (MH^+, 34%), 209 (MH^+-H_2O, 76), 191 (13), 182 (6), 163 (11), 149 (11), 135 (11), 122 (100), 111 (21), 97 (48), 81 (22), 67 (22), 55 (41), 45 (29). LC–HRMS: Found (M^+-H, $C_{13}H_{21}O_3$) 225.1510, calcd (M^+-H, $C_{13}H_{21}O_3$) 225.1496.
20. Data for ***RRS*-1**: 90% (GC). ^{1}H NMR data not given because of interfering impurities for complete interpretation. ^{13}C NMR (125 MHz, $CDCl_3$, Me_4Si): see Table 1. MS (EI) *m*/*z* (relative intensity): 227 (MH^+, 35%), 209 (MH^+-H_2O, 81), 191 (14), 182 (5), 164 (10), 147 (9), 135 (10), 122 (100), 107 (20), 97 (52), 83 (19), 67 (23), 55 (42), 45 (30). LC–HRMS: Found (M^+-H, $C_{13}H_{21}O_3$) 225.1503, calcd (M^+-H, $C_{13}H_{21}O_3$) 225.1496.