Diastereoselective Synthesis of Enantiopure γ-Butenolide-butyrolactones towards *Pseudopterogorgia* Lactone Furanocembranoid Substructures

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Abstract: A diastereoselective methodology for preparing *trans*-γ-lactone-γ-butenolides through vinylogous aldol additions of siloxyfuranes to enantiopure cyclopropylcarbaldehyde followed by a tin-catalyzed retroaldol–lactonization cascade is reported. This synthetic approach is applied to a short synthesis of an *exo*-trienol furan lactone substructure relevant to bielschowskysin and other related coral diterpenoid natural products.

Key words: marine furanocembranoids, asymmetric synthesis, vinylogous Mukaiyama addition, lactones, furans

Adjacently linked oxygenated heterocycles and γ-butyrolactone motifs are prominent substructures in a number of complex natural products. These moieties are present in various furanocembranoid diterpenes isolated from *Pseudopterogorgia* species such as **1**–**3**.[1] The segments highlighted (Figure 1) feature a 2,5-dihydrofuran or furan ring attached to a 4,5-disubstituted butyrolactol or butyrolactone. With special attention to diterpenoids **1** and **2**, strategies[2] towards the synthesis of these substructures have been developed motivated by the unique frameworks, intriguing biogenetic origins[3] and biological activity of the underlying natural products.

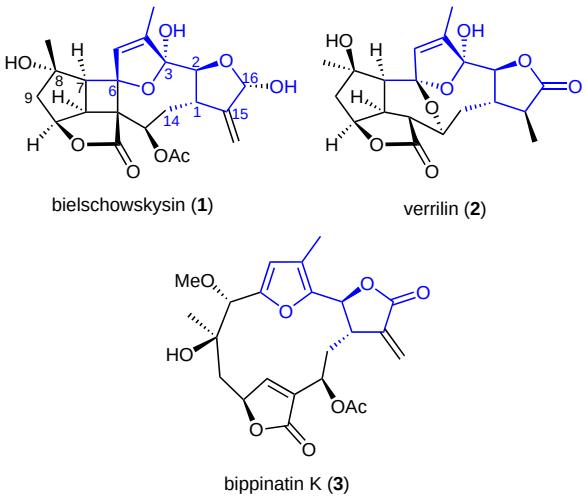

Figure 1 *Pseudopterogorgia* diterpenoids with 2,5-dihydrofuran, furan-linked butyrolactone, and butyrolactol framework

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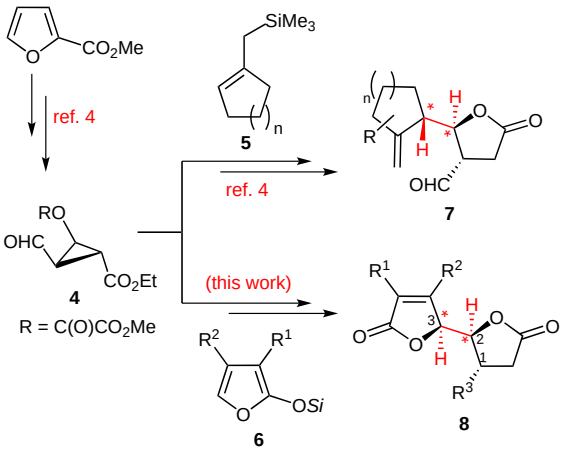
We report here the enantio- and diastereoselective synthesis of such substructures via a highly selective vinylogous aldol addition of 2-siloxyfurans **6** to enantiopure cyclopropylcarbaldehyde **4**, the latter being readily available from ethyl 2-furoate in a two-step sequence (Scheme 1).[4] Previous investigations from our group demonstrated the diastereoselective addition of allylsilanes **5** to **4**, leading after a retroaldol–lactonization sequence to **7** in stereopure form. We envisioned that the construction of *trans*-γ-lactone-γ-butenolides **8**, which appear to be suitable precursors for the synthesis diterpenoids **1**–**3**, can be achieved via Lewis acid catalyzed vinylogous Mukaiyama aldol addition[5] of **6** followed by our previously established retroaldol–lactonization protocol.[4]



Scheme 1

Our investigation was initiated by reacting 2-trimethylsiloxyfurans **6** with cyclopropane **4** in the presence of $BF_3 \cdot OEt_2$ (Table 1). Employing **6a**, good conversion and diastereoselectivity to **9a** was achieved based on TLC and ^1H NMR analysis of the crude, however, no attempts to purify and isolate this intermediate were made, but rather its direct conversion to lactone aldehyde **8a** was investigated. Substantial decomposition was observed when $Ba(OH)_2 \cdot 8H_2O$ or triethylamine, which has been successful in other transformations of this type,[4] were employed to initiate the retroaldol–lactonization cascade. Switching to Otera's catalyst[6] **10** in the presence of methanol or ethylene glycol smoothly afforded **8a** or **8b** with perfect *anti*

selectivity (C1/C2) and a 6:1 diastereoselectivity at C2/C3 (Table 1, entries 1 and 2). When the silyl group in **6** was switched to a TBS group, a substantial improvement in diastereoselectivity for the formation of **8b** (99:1) was observed (Table 1, entry 3). Having established the reaction sequence, several substituted siloxylated furan nucleophiles were investigated giving rise to **8c–f** in acceptable overall yields starting from **4** (Table 1, entries 4–7). Especially gratifying was that **8d**,[7] which is most relevant as a precursor towards **1**–**3**, was obtained as a single stereoisomer (>99:1 de, 65% yield). The relative and absolute stereochemistry of **8** was unambiguously established by X-ray crystal structure analysis (Figure 2 for **8d**)[8] and chiral ellipticity evidence.[9] The butenolides displayed negative and positive Cotton shifts for the π–π* and n–π* transitions, respectively, revealing M helicity ascribed to derivatives with *S* configuration at C3 (see the Supporting Information). Noteworthy, from the *anti* arrangement of substituents in the γ-butyrolactone moiety (C1/C2 in **8**), it is clear that addition pathways leading to the cyclopropyl carbinol butenolides **9** are identical with those of the cyclic allylsilanes in accordance with the Felkin–Anh paradigm (Scheme 2).[10]

Starting with butenolide-lactone **8d**, transformations directed towards the diterpenoids **1**–**3** were investigated. DIBAL-H reduction furnished lactol-furan **11** (63%, Scheme 3), which was reoxidized under Ley's conditions to afford furan lactone **12** quantitatively. Extension at the

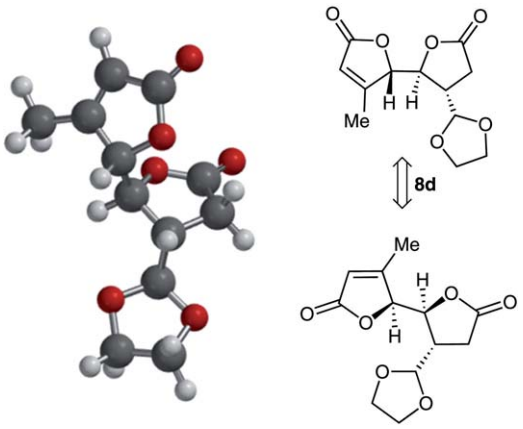
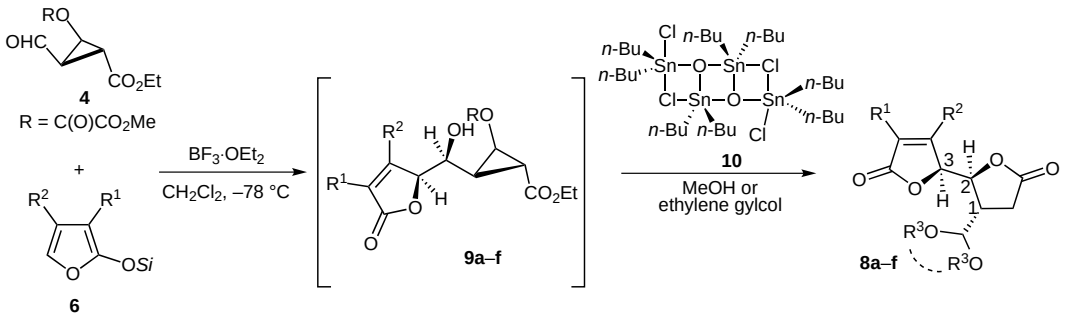


Figure 2 X-ray crystal structure of **8d**[8]

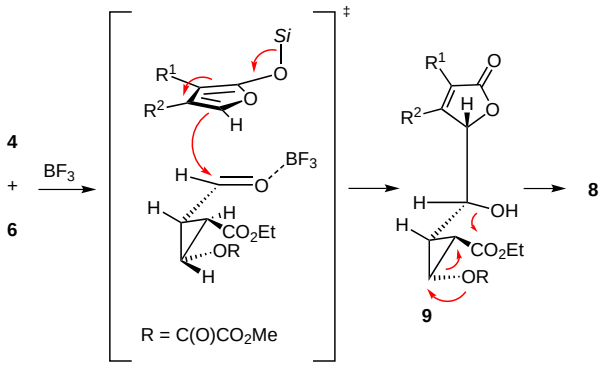
furan C6 with an additional aldehyde unit under Vilsmeier–Haack conditions was unsuccessful. A Heck-inspired Csp^2–Csp^2 coupling between the furan moiety of **12** and methacrylate ethyl ester under reaction conditions described by Miaura and co-workers[11] was next investigated. Treatment of a DMF solution of **12** with ethyl methacrylate, 5 mol% $Pd(OAc)_2$, LiOAc (4 equiv), and $Cu(OAc)_2 \cdot 5H_2O$ (2 equiv) afforded **13** (52% yield).[12] Noteworthy in this transformation was the preferential elimination of the β-hydrogen attached to the least hindered carbon (C9). Finally, oxidation of the furan moiety using bromine in methanol afforded **14** as a diastereomer-

Table 1 Butenolide-lactones **8** from Sequential Vinylogous Mukaiyama Aldol Reaction and Retro-Aldol–Lactonization Cascades



Entry	*Si*	R^1	R^2	Lactonization conditions[a]	R^3	Yield of **8** (%)	dr[b,c]
1	**6a** TMS	H	H	A	**8a** Me	38	83:17
2	**6a** TMS	H	H	B	**8b** $(CH_2)_2$	40	86:14
3	**6b** TBS	H	H	B	**8b** $(CH_2)_2$	40	99:1
4	**6c** TBS	Me	H	B	**8c** $(CH_2)_2$	44	87:13
5	**6d** TBS	H	Me	B	**8d** $(CH_2)_2$	65	>99:1
6	**6e** TBS	Ph	Ph	B	**8e** $(CH_2)_2$	42	91:9
7	**6f** TBS	4-*t*-BuPh	4-*t*-BuPh	B	**8f** $(CH_2)_2$	50	90:10

[a] A: catalyst **10** (5 mol%), MeOH, reflux, 12 h; B: catalyst **10** (5 mol%), ethylene glycol, PhMe, reflux, 12 h.
[b] Ratio of 1*S*,2*S*,3*S* and 1*S*,2*S*,3*R* diastereomers.
[c] Determined by ^1H NMR integral analysis.



Scheme 2 Stereochemical model for the formation of **9** followed by retroaldol–lactonization cascade to **8**

ic mixture of dimethoxylated products which, upon treatment on silica, gave lactone **15**.[13] The *Z* configuration of the newly formed alkene moiety was unambiguously assigned based on the H5/H7 NOESY correlation. Thus, the *exo*-olefinated dihydrofuran moiety being useful as a potential precursor for **1** and in core structures of other diterpenoidal natural products such as **16**[14] can be easily accessed through the aforementioned oxidative transformation utilized in this study.

In conclusion, we have developed a new stereoselective strategy for constructing butenolide-butyrolactone and furan-butyrolactone units present in complex natural product structures such as **1**–**3** through vinylogous Mukaiyama addition of heterosiloxydienes to highly functionalized cyclopropane carbaldehyde **4** and a lactonization sequence, demonstrating in a new way the power of donor–acceptor-substituted cyclopropane building blocks.[15] In addition, the synthesis of a (*Z*)-*exo*-trienolfuran lactone substructure **15** representing the northeastern sector of bielschowskysin (**1**) was accomplished.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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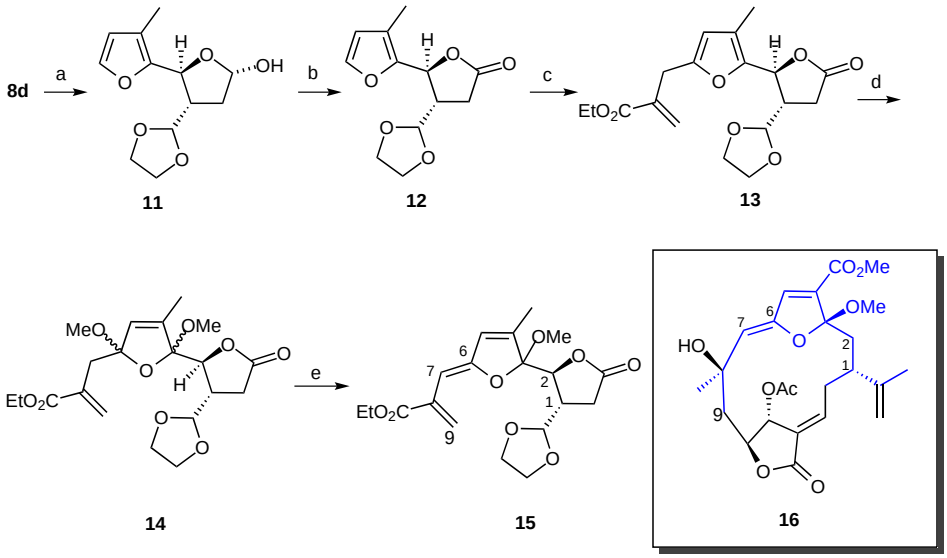

Scheme 3 *Reagents and conditions*: (a) DIBAL-H, THF, –78 °C, 63%; (b) TPAP, NMO, MS 4 Å, DMF, r.t., quant.; (c) ethyl methacrylate, $Pd(OAc)_2$, LiOAc, $Cu(OAc)_2 \cdot 5H_2O$, DMF, 117 °C, 52%; (d) Br_2, MeOH, NH_3 (g), –40 °C; e) column chromatography (silica gel), 55%

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(7) **Representative Procedure for Butenolide-Lactone Synthesis (8d)**
Under a nitrogen atmosphere, $BF_3{\cdot}OEt_2$ (0.28 mL, 2.21 mmol) was added via syringe to a solution of cyclopropylcarboxaldehyde (+)-**4** (500 mg, 2.01 mmol) in anhyd CH_2Cl_2 (20 mL) at –78 °C. After stirring for 30 min, a solution of **6d** in CH_2Cl_2 (2.11 mmol) was added slowly, resulting in an orange-colored solution. After stirring for 16 h at –78 °C, sat. aq $NaHCO_3$ (45 mL) was added, and the mixture was allowed to warm to r.t. The layers were separated, and the aqueous layer was extracted three times with EtOAc (45 mL each). The combined organic layers were washed with brine (45 mL), H_2O (45 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo to give the carbinol cyclopropane **9d** which was used for the next step without further purification. A round-bottomed flask, equipped with Dean–Stark trap was charged with crude cyclopropyl carbinol **9d** (approx. 1 equiv) followed by ethylene glycol (224 μL, 4.02 mmol, 2 equiv) and Sn catalyst **10** (5 mol%). The mixture was gently refluxed for 12 h, after which the crude mixture was evaporated and purified by chromatography on silica gel (EtOAc–hexanes = 3:1) to furnish compound **8d**.
(2*S*,3*S*,2′*S*)-3-[1,3]Dioxolan-2-yl-3′-methyl-3,4-dihydro-2*H*,2′*H*-[2,2′]bifuranyl-5,5′-dione (8d)
Yield 331 mg (65%), $[\alpha]_D^{25}$ +3.6 (*c* 0.3, MeOH), colorless crystals, mp 97–98 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.87 (m, 1 H), 4.94 (d, *J* = 4.1 Hz, 2 H), 4.69 (dt, *J* = 11.7, 5.8 Hz, 1 H), 4.10–3.86 (m, 4 H), 3.03 (td, *J* = 9.9, 4.4 Hz, 1 H), 2.79 (m, 1 H), 2.49 (dd, *J* = 18.0, 5.4 Hz, 1 H), 2.16 (dd, *J* = 12.3, 1.0 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 175.1, 172.2, 164.3, 118.3, 103.3, 84.5, 75.7, 65.8, 40.1, 29.4, 14.0. HRMS (EI): *m/z* calcd for $C_{12}H_{13}O_6$ 253.0712 $[M - H]^+$; found: 253.0710. IR (neat): 2932, 2902, 2864, 1779, 1730, 1646, 1402, 1266, 1188, 1147, 1089, 1019, 975, 899 cm^{-1}.

(8) Details on this X-ray crystal structure can be obtained from the Cambridge Crystallographic Data Center quoting CCDC 901653; see also the Supporting Information.

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(12) A mixture of **12** (50 mg, 0.21 mmol), ethyl methacrylate (105 μL, 0.84 mmol), $Pd(OAc)_2$ (2.4 mg, 0.011 mmol), $Cu(OAc)_2{\cdot}H_2O$ (84 mg, 0.42 mmol), and LiOAc (55 mg, 0.84 mmol) was stirred in DMF (1 mL) at 117 °C under air. After cooling, the reaction mixture was extracted with EtOAc and dried (Na_2SO_4). Compound **13** was purified by preparative reversed-phase HPLC using a gradient-elution method with increasing amounts of MeCN in H_2O.
2-{(2′*S*,3′*S*)-3′-[1,3]Dioxolan-2-yl-3-methyl-5′-oxo-2′,3′,4′,5′-tetrahydro[2,2′]bifuranyl-5-ylmethyl}acrylic Acid Ethyl Ester (13)
Yield 38 mg (52%). $[\alpha]_D^{25}$ +54.4 (c 0.4, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.24 (t, *J* = 3.3 Hz, 1 H), 5.91 (s, 1 H), 5.52 (t, *J* = 4.2 Hz, 1 H), 5.41 (m, 1 H), 4.92 (t, *J* = 3.9 Hz, 1 H), 4.22 (m, 2 H), 4.05–3.87 (m, 4 H), 3.57 (d, 2 H), 3.13 (m, 1 H), 2.87 (m, 1 H), 2.63 (m, 1 H), 2.03 (t, 3 H), 1.30 (t, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.9, 165.8, 152.1, 143.0, 135.9, 125.5, 119.8, 109.5, 101.6, 72.2, 64.3, 59.4, 41.2, 29.6, 28.3, 13.0, 8.9. HRMS (EI): *m/z* calcd for $C_{18}H_{22}O_7$ $[M]^+$: 350.1366; found: 350.1364. IR (neat): 2962, 2904, 1779, 1714, 1634, 1406, 1260, 1196, 1024, 947, 795 cm^{-1}.

(13) A solution of **13** (15 mg, 0.042 mmol) in a mixture of MeOH (50 μL) and Et_2O (35 μL) was stirred and cooled to –40 °C. Bromine (7.1 μL, 0.044 mmol) in dry MeOH (0.1 mL) was added dropwise over 5 min. After addition, stirring was continued for an additional 10 min. The mixture was saturated with NH_3 gas to pH 8, allowed to warm to r.t., diluted with Et_2O and concentrated. The residue was purified by flash chromatography (silica gel, 1:1 EtOAc–hexanes) to afford a 1:1 mixture of **15** and 3-*epi*-**15**.
2-[(2*S*,2′*S*,3′*S*)-3′-[1,3]Dioxolan-2-yl-2-methoxy-3-methyl-5′-oxo-2′,3′,4′,5′-tetrahydro-2*H*-[2,2′]bifuranyl-(5*Z*)-ylidenemethyl]acrylic Acid Ethyl Ester (15)
Yield 8.8 mg, 55%. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.34 (s, 1 H), 6.18 (q, *J* = 1.4 Hz, 1 H), 5.41 (d, *J* = 5.1 Hz, 1 H), 4.85 (d, *J* = 3.5 Hz, 1 H), 4.50 (d, *J* = 2.1 Hz, 1 H), 4.28–4.18 (m, 2 H), 4.00–3.85 (m, 4 H), 3.47 (s, 2 H), 3.14 (s, 2 H), 2.84 (m, 1 H), 2.68 (m, 1 H), 2.42 (m, 1 H), 1.95 (s, 3 H), 1.31 (t, *J* = 3.2 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 176.7, 166.9, 157.6, 141.2, 133.7, 127.1, 124.1, 115.0, 103.9, 94.0, 81.1, 65.8, 61.3, 50.9, 50.4, 38.4, 28.9, 14.1, 12.4. HRMS (EI): *m/z* calcd for $C_{19}H_{24}O_8$ $[M]^+$: 380.1471; found: 380.1478. IR (neat): 2904, 1782, 1710, 1636, 1447, 1366, 1244, 1130, 1021, 957, 942, 852 cm^{-1}.

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