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Regiospecific synthesis of cepanolide, a cancer chemoprotective micronutrient found in green onions

John Boukouvalas *, Vincent Albert

Département de Chimie, Pavillon Alexandre-Vachon, Université Laval, 1045 Avenue de la Médecine, Quebec City, Quebec, Canada G1V 0A6

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ABSTRACT

The naturally occurring γ-hydroxy-β-sulfanylbutenolide cepanolide and a range of new analogues were synthesized in concise, regiospecific manner through the combined use of 2-silyloxyfuran oxyfunctionalization and tandem thio-Michael addition/elimination.

Compelling evidence from epidemiologic studies indicates that individuals who consume copious amounts of *Allium* vegetables (e.g., onions and garlic) reduce their susceptibility to cancer at a variety of organ sites.[1] The protective effects of *Alliums* have been largely attributed to their content of organosulfur compounds (OSCs), as exemplified by diallyl sulfide (DAS) and diallyl disulfide (DADS, Fig. 1).[2] Indeed, both DAS and DADS have been shown to confer protection against chemical-induced carcinogenesis in animal models.[3] A major mechanism by which OSCs are believed to inhibit carcinogenesis involves upregulation of phase II detoxifying enzymes, such as quinone reductase (QR) and glutathione S-transferase (GST).[4] Thus, phase II enzyme induction has emerged as a promising strategy for cancer chemoprevention.[5]

In 2007, Xiao and Parkin reported the discovery of a new QR-inducer from *Allium cepa* (green onion) that we now name cepanolide (**1**, Fig. 1).[6] In murine hepatoma cells, cepanolide increased QR activity up to 6-fold (CD = 15.6 μg/mL) and was also capable of doubling GST activity at higher concentrations.[6] The combination of potentially useful biological properties, low natural abundance (0.0006% of dry onion weight) and unusual structure, renders **1** an attractive target for synthesis. Additionally, the favorable physicochemical properties of **1** (MW 188, CLogP 0.80) make it an excellent starting point for structural optimization through analogue synthesis.[7]

Recently, the groups of Paul and Ordónez synthesized **1** along with its isomer **2** by two related pathways (5–6 steps) that ultimately involve borohydride reduction of anhydride **3** (Scheme 1).[8] Notwithstanding the modest regioselectivity of this reaction, the identity of the major isomer (**1**) was unambiguously established

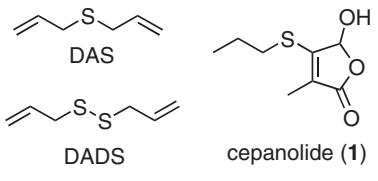
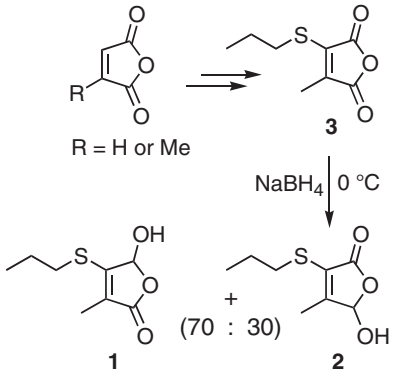


Figure 1. Structures of *Allium* OSCs.



Scheme 1. Previous synthesis of cepanolide.[8]

* Corresponding author. Tel.: +1 418 656 5473; fax: +1 418 656 7916.
E-mail address: john.boukouvalas@chm.ulaval.ca (J. Boukouvalas).

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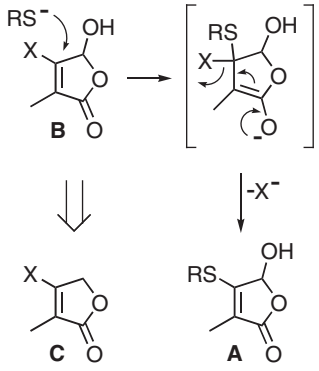
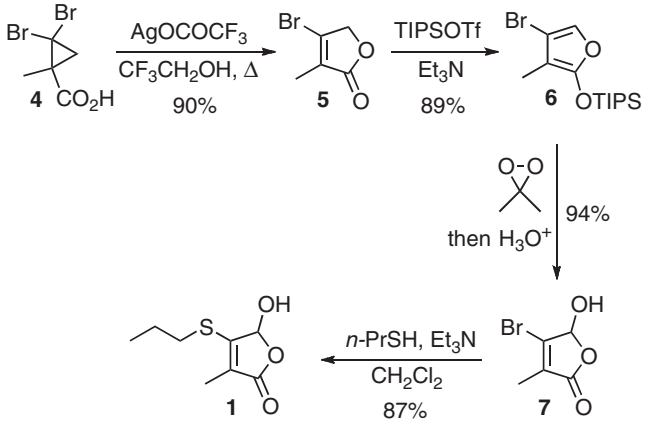


Scheme 2. Our synthetic strategy.



Scheme 3. Regiospecific synthesis of cepanolide (**1**).

by X-ray analysis,[8] thereby also confirming the originally proposed structure of cepanolide.

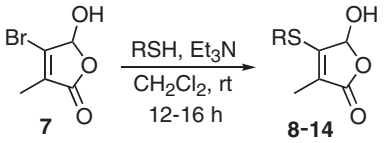
We now describe a distinctly different synthetic approach that is inherently regiospecific and amenable to analogue production. As outlined in Scheme 2, cepanolide and its analogues (cf. **A**) would derive from unprotected hydroxybutenolide **B** by means of tandem thio-Michael addition/elimination. Although related reactions of γ-alkoxy-β-halobutenolides have been described in the literature,[9] little is known on the behavior of the corresponding hydroxybutenolides toward thiolates.[10] Nonetheless, we felt that the comparatively high acidity of alkyl thiols (pK_a 10–11) should alleviate the need of protecting the hydroxyl group of **B**, which would in turn derive from **C** by the application of our oxyfunctionalization method.[11,12]

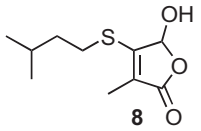
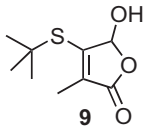
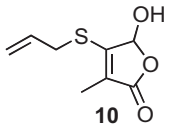
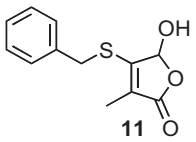
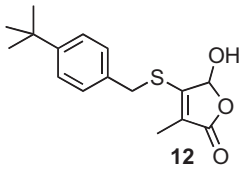
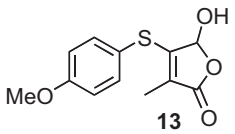
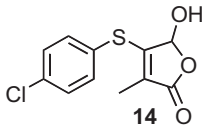
The synthesis began from commercially available or easily prepared[13] 2,2-dibromo-1-methylcyclopropanecarboxylic acid (**4**, Scheme 3). Acid **4** was converted to bromobutenolide **5** with high efficiency using the operationally simple procedure of Sydnes.[14,15] Silylation of **5** with TIPSOTf/Et_3N in dichloromethane (1 h, 0 °C) afforded 2-silyloxyfuran **6** in an unoptimized yield of 89% after flash chromatography.[16] Sequential treatment of **6** with an acetone solution of dimethyldioxirane and a few drops of water/Amberlyst 15,[11] provided the desired hydroxybutenolide **7** in excellent yield.[17] This highly crystalline building block could be stored at room temperature for several months without any signs of decomposition.

With easy access to **7**, the displacement of bromide ion by thiolate was briefly examined. Among the conditions tried, the simplest and most effective consisted in the use of a slight excess of *n*-PrSH/Et_3N in dichoromethane at room temperature. In this manner, analytically pure cepanolide (**1**) was obtained in 87% yield after flash chromatography (Scheme 3).[18] Prompted by the efficiency of this process, its scope and preparative value were further investigated by the synthesis of a small library of unnatural cepanolide analogues (Table 1).[19] Remarkably, yields were excellent across the whole range of alkyl, allyl, benzyl and aryl thiols tried, including the highly hindered *t*-BuSH (entry 2).

In conclusion, a regiospecific synthesis of the naturally occurring phase II enzyme inducer cepanolide has been achieved in four steps and 66% overall yield from commercially available 2,2-dibromo-1-methylcyclopropanecarboxylic acid. The inherent flexibility of this route along with a new protocol for constructing γ-hydroxy-β-sulfanylbutenolides were further demonstrated by the expedient preparation of a range of unnatural cepanolide analogues. With unfettered synthetic access to such densely functionalized OSCs, the stage is now set for more thorough biological evaluation in vitro and in vivo.

Table 1
Synthesis of cepanolide analogues



Entry	Product	Yield[a] (%)
1	 **8**	92
2	 **9**	84
3	 **10**	82
4	 **11**	89
5	 **12**	83
6	 **13**	91
7	 **14**	84

[a] Isolated yield after column chromatography.

Acknowledgments

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16. The silica gel was pretreated with Et_3N/hexanes before use. *Data for silyloxyfuran* ***6***: colorless oil, R_f 0.62 (hexanes); IR (NaCl, film): 2946, 2869, 1647, 1531, 1464, 1412, 1374, 1265, 1091, 1027, 927, 883, 848, 681 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.84 (s, 1H), 1.82 (s, 3H), 1.28–1.19 (m, 3H), 1.08 (d, J = 7.2 Hz, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.6, 128.8, 104.7, 93.4, 17.7, 12.5, 7.6; HRMS (ESI): Calcd for $C_{14}H_{25}O_2BrSi$ (m/z): 332.0831, Found: 332.0807.
17. *Data for hydroxybutenolide* ***7***: white solid (mp 90–92 °C), R_f 0.37 (40% EtOAc/hexanes); IR (NaCl, film): 3244, 2922, 1733, 1653, 1456, 1331, 1280, 1176, 1117, 1062, 950, 839, 750 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.00 (s, 1H), 4.81 (br s, 1H), 1.92 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.9, 141.3, 132.2, 98.0, 10.4; HRMS (ESI): Calcd for $C_5H_5O_3Br$ (m/z): 191.9427, Found: 191.9422.
18. *Synthesis of cepanolide (****1****)*: To a solution of hydroxybutenolide **7** (30.3 mg, 0.157 mmol) in dichloromethane (0.5 mL), 1-propanethiol (23 μL, 0.251 mmol, 1.6 equiv) and triethylamine (46 μL, 0.330 mmol, 2.1 equiv) were successively added at rt. After stirring for 15 h at rt, the volatiles were evaporated under reduced pressure. Flash chromatography on silica gel (25% EtOAc in hexanes) afforded **1** as a white solid (25.8 mg, 87% yield); mp 65–69 °C, R_f 0.30 (30% EtOAc/hexanes); IR (NaCl, film): 3296, 2969, 2918, 1734, 1626, 1457, 1281, 1142, 1072, 961, 864, 750 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.05 (s, 1H), 3.72 (br s, 1H), 3.08 (t, J = 8.0 Hz, 2H), 1.85 (s, 3H), 1.77–1.67 (m, 2H), 1.05 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 157.5, 123.2, 96.4, 32.6, 23.7, 13.4, 9.4; HRMS (ESI): Calcd for $C_8H_{12}O_3S$ (m/z): 188.0515, Found: 188.0507; Anal. Calcd for $C_8H_{12}O_3S$: C, 51.04; H, 6.43; S, 17.03. Found: C, 50.91; H, 6.60; S, 16.93.
19. *Data for cepanolide analogues (****8****–****14****)*: Compound **8**: mp 66–68 °C, IR (NaCl, film): 3343, 2958, 2925, 2871, 1732, 1622, 1468, 1295, 1153, 1065, 957, 864, 751, 631 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.07 (s, 1H), 3.11 (t, J = 8.0 Hz, 2H), 1.82 (s, 3H), 1.76–1.69 (m, 1H), 1.58–1.53 (m, 2H), 0.94 (d, J = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 158.0, 122.8, 96.7, 39.0, 28.8, 27.6, 22.4, 9.4; HRMS (ESI): Calcd for $C_{10}H_{16}O_3S$ (m/z): 216.0835, Found: 216.0820. Compound **9**: mp 94–97 °C, IR (NaCl, film): 3271, 2994, 2967, 2926, 2865, 1758, 1732, 1628, 1459, 1368, 1345, 1295, 1162, 1124, 1061, 1044, 956, 848 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.15 (s, 1H), 4.18 (br s, 1H), 1.94 (s, 3H), 1.49 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 155.1, 133.6, 98.3, 49.9, 32.7, 10.5; HRMS (ESI): Calcd for $C_9H_{14}O_3S$ (m/z): 202.0669, Found: 202.0664. Compound **10**: mp 77–79 °C, IR (NaCl, film): 3340, 3086, 2979, 2923, 2858, 1756, 1622, 1434, 1343, 1297, 1152, 1128, 1064, 1044, 958, 863, 751, 633 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.12 (s, 1H), 5.94–5.85 (m, 1H), 5.34 (d, J = 16.8 Hz, 1H), 5.23 (d, J = 10.0 Hz, 1H), 3.88 (dd, J = 14.4, 8.0 Hz, 1H), 3.63 (dd, J = 14.4, 5.8 Hz, 1H), 1.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 157.2, 133.3, 123.7, 119.3, 96.6, 33.6, 9.4; HRMS (ESI): Calcd for $C_8H_{10}O_3S$ (m/z): 186.0332, Found: 186.0351. Compound **11**: mp 110–113 °C, IR (NaCl, film): 3331, 2923, 2853, 1732, 1622, 1455, 1295, 1153, 1127, 1068, 958, 751, 706 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39-7.28 (m, 5H), 5.98 (s, 1H), 4.34 (s, 2H), 1.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 156.7, 136.1, 129.2, 129.0, 128.3, 123.7, 96.5, 35.1, 9.4; HRMS (ESI): Calcd for $C_{12}H_{12}O_3S$ (m/z): 236.0515, Found: 236.0507. Compound **12**: mp 96–99 °C, IR (NaCl, film): 3336, 2963, 2868, 1733, 1622, 1464, 1292, 1151, 1065, 960, 752 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, J = 8.8 Hz, 2H), 7.30 (d, J = 8.8 Hz, 2H), 6.02 (s, 1H), 4.93 (br s, 1H), 4.33 (s, 2H), 1.80 (s, 3H), 1.31 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 157.8, 151.3, 133.0, 128.7, 126.1, 122.8, 96.8, 34.8, 34.7, 31.5, 9.4; HRMS (ESI): Calcd for $C_{16}H_{20}O_3S$ (m/z): 292.1152, Found: 292.1133. Compound **13**: mp 66–68 °C, IR (NaCl, film): 3364, 2925, 2853, 1732, 1626, 1592, 1495, 1291, 1251, 1175, 1152, 1029, 955, 831, 711, 640 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, J = 9.2 Hz, 2H), 6.91 (d, J = 9.2 Hz, 2H), 5.65 (s, 1H), 3.83 (s, 3H), 1.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 161.3, 157.6, 137.3, 123.3, 117.6, 115.2, 96.4, 55.7, 9.3; HRMS (ESI): Calcd for $C_{12}H_{12}O_4S$ (m/z): 252.0475, Found: 252.0456. Compound **14**: mp 136–138 °C, IR (NaCl, film): 3378, 3098, 2924, 2863, 1742, 1627, 1479, 1430, 1333, 1289, 1153, 1133, 1091, 1060, 1039, 1010, 956, 821 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, J = 8.8 Hz, 2H), 7.38 (d, J = 8.8 Hz, 2H), 5.71 (s, 1H), 3.41 (br s, 1H), 1.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 155.5, 136.7, 136.4, 130.0, 126.1, 125.5, 96.2, 9.6; HRMS (ESI): Calcd for $C_{11}H_9O_3ClS$ (m/z): 255.9971, Found: 255.9961.