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Registry No. Bryostatin 3, 87370-86-3.

A Direct Synthesis of β-Hydroxybutyrolactones: Total Synthesis of Dendrolasin and Formal Total Synthesis of Aplysistatin

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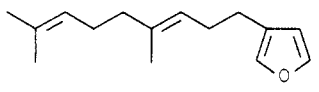
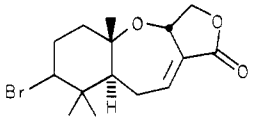
The β-hydroxybutyrolactone unit has been employed as a building block for the synthesis of several furans and sesquiterpenes. Negishi and co-workers[1] developed a clever route to dendrolasin (1). Recently Prestwich and Shieh[2]



1



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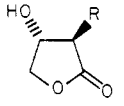
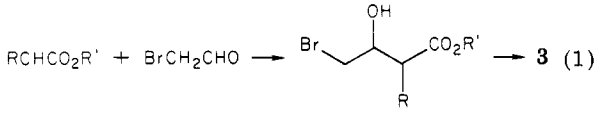


3

3a, R = $(CH_3)_2C{=}CH(CH_2)_2C(CH_3){=}CH(CH_2)_2$-

reported an elegant synthesis of aplysistatin (2) that used **3a** as a key intermediate. The utility of **3** has been enhanced by a study of the alkylation chemistry of its dianion[3] and by advances in the synthesis of **3**.[4] We recently developed a convenient synthesis of anhydrous bromoacetaldehyde[5] and now report the use of this reagent for the synthesis of several β-hydroxybutenolides. The overall plan is depicted in eq 1.

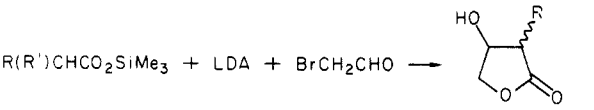


$$RCHCO_2R' + BrCH_2CHO \longrightarrow \text{4} \longrightarrow \mathbf{3} \quad (1)$$

4

While the anions of the ethyl esters of aliphatic acids[6] reacted rapidly with bromoacetaldehyde to produce **4** (R′ = Et), the hydrolysis resulted in complex product mixtures. Presumably competitive formation of an epoxy ester and its subsequent base-mediated transformations were responsible. The reaction of carboxylic acid dianions[7] with bromoacetaldehyde failed due to the polymerization of the bromoacetaldehyde. Although the *tert*-butyl ester anions afforded the β-hydroxy esters **4** in good yields, subsequent attempts to remove the *tert*-butyl group (pTSA, PhH ↑↓; Me_3SiI, CH_2Cl_2) resulted in only modest yields of the desired bromo hydroxy acid. In contrast, the trimethylsilyl ester anions[6] afforded a mixture of **3** and **5** (eq 2). The

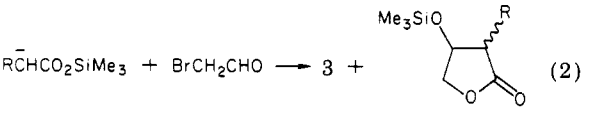
Table I. Synthesis of β-Hydroxybutyrolactones



$$R(R')CHCO_2SiMe_3 + LDA + BrCH_2CHO \longrightarrow$$

entry	R	R′	yield, %
1	CH_3	CH_3	61
2	*n*-Bu	H	90
3	$H_2C{=}CHCH_2$	H	62[b]
4	C_6H_5O	H	80
5	C_6H_5S	H	65[a]
6	C_6H_5Se	CH_3	75
7	Br	Br	
8	$H(CH_2C(CH_3){=}CHCH_2)_2CH_2$	H	99

[a] A 30% yield of the corresponding butenolide was also obtained. [b] Entry 3 was previously prepared in ref 3b.

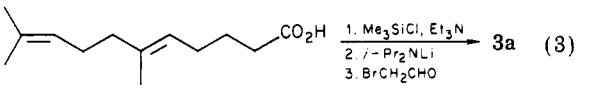


$$R\bar{C}HCO_2SiMe_3 + BrCH_2CHO \longrightarrow \mathbf{3} + \text{5} \quad (2)$$

5

complete conversion to **3** could be effected by quenching the reaction with tetra-*n*-butylammonium fluoride. The results are illustrated in Table I.

Most silyl esters were converted to **3** in good to excellent yields. However, if the substituent R was one that increased the acidity of the α-proton (entry 5), varying amounts of the corresponding butenolide were obtained. The hydroxybutenolides were initially produced as an equal mixture of diastereomers but could be converted to the trans isomer.[9] The synthesis of the key intermediate in the Prestwich synthesis of aplysistatin is shown in eq 3. Acid **6**[8] was converted to its trimethylsilyl ester and



$$\text{6} \xrightarrow[2.\ i\text{-}Pr_2NLi\ \ 3.\ BrCH_2CHO]{1.\ Me_3SiCl,\ Et_3N} \mathbf{3a} \quad (3)$$

6

was reacted sequentially with lithium diisopropylamide (LDA) and bromoacetaldehyde to provide **3a** as an equal mixture of diastereomers in 99% yield. One of the diastereomers was identical with authentic sample. The hydroxy lactone **3a** was dehydrated to the butenolide and then reduced with diisobutylaluminum hydride.[10] Acidic workup of the reduction furnished dendrolasin (1) in 32% yield from **3a** (eq 4).

$$\mathbf{3a} \xrightarrow[2Et_3N]{CH_3SO_2Cl} \xrightarrow[\text{then } H^+]{(i\text{-}Bu)_2AlH} \mathbf{1} \quad (4)$$

Since higher molecular weight α-bromoaldehydes are readily available, the approach described herein should permit the synthesis of several butenolides, hydroxybutyrolactones, and tetronic acids. The synthesis of **3a** constitutes a formal total synthesis of aplysistatin.

Experimental Section

General Experimental Procedure for Synthesis of 3. To a dry flask containing a nitrogen atmosphere was added 1 mL of dry THF (distilled from $LiAlH_4$) and 0.15 mL of diiso-

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propylamine (1.1 mol). The solution was cooled to 0 °C, and 0.54 mL of *n*-butyllithium (2.05 M in hexane) was added dropwise. After 15 min the solution was cooled to −78 °C and a 1 M solution of the silyl ester (1.0 mmol) in THF was added dropwise. After the reaction solution was stirred for 30 min, 1.1 mL of a 1 M solution of $BrCH_2CHO$ in THF was added at once. After being stirred for 5 min, the reaction was quenched with 0.13 mL (2.3 mmol) of acetic acid and the resultant suspension was warmed to 0 °C. A saturated solution of aqueous $NaHCO_3$ (3 mL) was added, and the two-phase system was stirred vigorously for 5 h. The ice bath was allowed to warm to ambient temperature. The reaction mixture was diluted with brine (5 mL) and was extracted with 3 × 10 mL of Et_2O. The organic phase was dried over Na_2SO_4. Upon removal of solvent some silylated material was present. Complete conversion to the hydroxy lactone was accomplished by dissolving the crude product in 3 mL of methylene chloride and adding ca. 0.5 mL of a 1 M solution of tetra-*n*-butylammonium fluoride in THF. The reaction was stirred at ambient temperature until TLC analysis showed disappearance of high R_f material (15–20 min). The solution was diluted with 5 mL of Et_2O and washed with 1 × 3 mL of water and 1 × 3 mL of brine. The aqueous layers were combined and reextracted with 3 mL of ether. The ethereal layer was dried over Na_2SO_4. Purification was effected by filtration through a small amount of silica gel with ethyl ether.

Entry 1: IR (film) 3460, 2970, 1770, 1100 cm^{-1}; 60-MHz NMR ($CDCl_3$) δ 1.23 (s, 6 H), 3.92–4.50 (m, 4 H); high-resolution mass spectrum for $C_6H_{10}O_3$ requires *m/e* 130.063 00, found 130.063 35.

Entry 2: IR (film) 3460, 2960, 1775, 1170 cm^{-1}; NMR ($CDCl_3$) δ 0.93 (br, 3 H), 1.12–2.00 (m, 9 H), 2.30–2.62 (m, 1 H), 3.90 (br s, 1 H), 4.00–4.67 (m, 3 H); high-resolution mass spectrum for $C_8H_{13}O_3$ ($M^+ - 1$) requires *m/e* 157.086 47, found 157.086 88.

Entry 3: IR (film) 3460, 2970, 1780, 1255, 840 cm^{-1}; NMR ($CDCl_3$) 2.3–2.7 (m, 3 H), 3.63 (br s, 1 H), 4.0–4.6 (m, 3 H), 4.92–5.32 (m, 2 H), 5.50–6.20 (m, 1 H); high-resolution mass spectrum for $C_7H_{10}O_3$ requires *m/e* 142.063 00, found 142.063 52.

Entry 4: IR (film) 3490, 1770, 1165, 750, 690 cm^{-1}; NMR ($CDCl_3$) δ 3.20 (br s, 1 H), 3.80–4.30 (m, 4 H), 6.70–7.30 (m, 5 H).

Entry 5: IR (film) 3460, 1780, 1590, 1490, 1230, 1100, 905, 725 cm^{-1}; NMR ($CDCl_3$) δ 3.62 (br s, 1 H), 4.0–5.0 (m, 4 H), 6.80–7.50 (m, 5 H).

Entry 6: IR (film) 3440, 2980, 1770, 1020, 740 cm^{-1}; NMR ($CDCl_3$) δ 1.58 (s, 3 H), 3.81 (br s, 1 H)8 4.10–4.40 (m, 3 H), 7.10–7.80 (m, 5 H); high-resolution mass spectrum for $C_{11}H_{12}O_3Se$ requires *m/e* 271.995 12, found *m/e* 271.995 62.

Entry 8. The isomers were separated by flash chromatography using 3:1 ether:hexane. Trans isomer: IR (film) 3460, 2940, 1770, 1180, 1025 cm^{-1}; 300-MHz NMR ($CDCl_3$) δ 1.62 (br s, 6 H), 1.70 (br s, 3 H), 1.80–2.30 (m, 8 H), 2.48 (m, 1 H), 3.09 (br s, 1 H), 4.00–4.60 (m, 3 H), 5.12 (br t, 2 H); high-resolution mass spectrum for $C_{15}H_{24}O_3$ requires *m/e* 252.172 55, found 252.173 09. Cis isomer: IR (film) 3460, 2930, 1765, 1450, 1275, 1140, 1040, 975 cm^{-1}; 300-MHz NMR ($CDCl_3$) δ 1.63 (br s, 9 H), 2.00 (m, 8 H), 2.40 (m, 1 H), 2.78 (br s, 1 H), 4.23 (d, 2 H), 4.47 (m, 1 H), 5.13 (br t, 2 H); high-resolution mass spectrum for $C_{15}H_{24}O_3$ requires *m/e* 252.172 55, found 252.173 67.

Dendrolasin (1). Compound **3a** (0.29 mmol) was dissolved in 1 mL of CH_2Cl_2 and cooled to 0 °C. Triethylamine (0.6 mmol) was added followed by addition of neat methanesulfonyl chloride (0.3 mmol). The reaction was stirred and allowed to warm slowly to room temperature over 5 h. The reaction was diluted with 5 mL of Et_2O and was washed once with 2 mL saturated $NaHCO_3$ (aqueous) and then once with brine. The organic layer was dried over Na_2SO_4. The crude butenolide was sufficiently pure to be taken to the next step. The butenolide (0.3 mmol) was dissolved in 3.5 mL of dry THF and was added to a flask containing a nitrogen atmosphere. After the solution was cooled to −20 °C, 0.40 mL of Dibal (1 M in hexane) was added dropwise. TLC analysis after 1 h revealed the disappearance of starting material. The reaction was quenched with 0.03 mL of acetic acid and was warmed to room temperature. After washing with 2 mL of saturated $NaHCO_3$ (aqueous) and 2 mL of brine, the organic phase was dried over Na_2SO_4. Removal of solvent left a viscous yellow oil, which contained small amounts of furan by NMR but a large OH stretch in the IR. This material was dissolved in 3 mL of CH_2Cl_2 and treated with a catalytic amount of pTSA·H_2O for 3 h until TLC analysis showed one major spot (R_f 0.85 in 1:1 Et_2O:hexane. The solution was diluted with hexane and filtered through 3 of silica gel with hexane. Removal of the solvent left 20.5 mg of a colorless oil, which was shown to be dendrolasin. This was obtained in 32% yield from **3a**. This was shown to be dendrolasin by comparison with literature data.[11]

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Registry No. **1**, 23262-34-2; **3a** (isomer 1), 87727-61-5; **3a** (isomer 2), 87727-62-6; **6**, 24120-56-7; $BrCH_2CHO$, 17157-48-1; $(CH_3)_2CHCO_2SiMe_3$, 16883-61-7; $BuCH_2CO_2SiMe_3$, 14246-15-2; $H_2C{=}CHCH_2CH_2CO_2SiMe_3$, 23523-56-0; $C_6H_5OCH_2CO_2SiMe_3$, 21273-08-5; $C_6H_5SCH_2CO_2SiMe_3$, 55724-31-7; $C_6H_5Se(CH_3)CHCO_2SiMe_3$, 87683-16-7; $Br_2CHCO_2SiMe_3$, 37977-60-9; $H(CH_2C(CH_3){=}CHCH_2)_2CH_2CH_2CO_2SiMe_3$, 87683-17-8; α,α-dimethyl-β-hydroxybutyrolactone, 87683-09-8; α-butyl-β-hydroxybutyrolactone, 87683-10-1; α-allyl-β-hydroxybutyrolactone, 87683-11-2; α-phenoxy-β-hydroxybutyrolactone, 87683-12-3; α-(phenylthio)-β-hydroxybutyrolactone, 87683-13-4; α-(phenylseleno)-α-methyl-β-hydroxybutyrolactone, 87683-14-5; α,α-dibromo-β-hydroxybutyrolactone, 87683-15-6; α-(4,8-dimethyl-3,7-nonadienyl)-β-hydroxybutyrolactone, 87727-60-4.

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Formation of *trans*-Stilbenes from 1,1-Dichloro-2,2-diarylethanes: A New Cobaloxime-Mediated Carbenoid Rearrangement

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Organocobalt compounds with a rigid planar ligand system have attracted considerable attention as model systems for vitamin B_{12}.[1] Among these, bis(dimethylglyoximato)cobalt(I) ("cobaloxime", **1**) is perhaps one of the best known. Interest in alkylcobaloximes has been steadily growing due to their use as models for biological systems and as intermediates in interesting synthetic transformations.[2] Investigations have concentrated mainly on alkylcobaloximes obtained by displacement of organic halides by the "supernucleophilic" Co(I) species. The ready homolysis of the Co–C bond in these compounds has been synthetically exploited, and a number of radical displacements,[3] couplings,[4] and rearrangements[5] have been reported. In comparison to the wealth of information regarding the interaction of bis(dimethylglyoximato)cobalt (I) with alkyl halides, very little is known about the re-

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