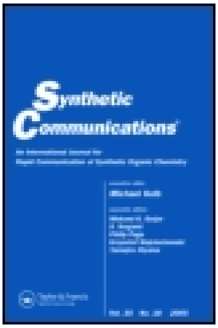

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

A Concise and Efficient Novel Synthesis of Cleviolide

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To cite this article: Renzo Rossi, Fabio Bellina & Matteo Biagetti (1999): A Concise and Efficient Novel Synthesis of Cleviolide, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 29:19, 3415-3420

To link to this article: http://dx.doi.org/10.1080/00397919908085969

SYNTHETIC COMMUNICATIONS, 29(19), 3415-3420 (1999)

A CONCISE AND EFFICIENT NOVEL SYNTHESIS OF CLEVIOLIDE[1]

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Abstract: Cleviolide **1** has been synthesized in 73 % overall yield by a short reaction sequence involving the preparation of 4-methyl-1-trimethylsilylpent-3-en-1-yne **7** from trimethylsilylethynylzinc chloride **6** and 1-bromo-2-methylpropene **5**, the direct conversion of **7** into the corresponding 1-tributylstannyl derivative **8** and the Pd-catalysed reaction of this organotin derivative with 4-bromofuran-2(5*H*)-one **10**.

In connection with ongoing projects relating to the development of new and convenient procedures for the selective synthesis of natural and unnatural biologically active five-membered unsaturated lactone derivatives,[2] we recently became interested in the synthesis of cleviolide **1**, an acetylenic monoterpene furan-2(5*H*)-one which was isolated from *Senecio clevelandii* by Bohlmann *et al*[3] and represents a precursor to both (*Z*)- and (*E*)-stereoisomers of scobinolide (*cis*- and *trans*-dihydrocleviolide) **2a** and **2b**, respectively,[4] two other monoterpene lactones isolated from *S. clevelandii*[3] and *Psathyrella scobinacea*.[5] In fact, the biological activity of compound **1** has not been evaluated yet. On the other hand,

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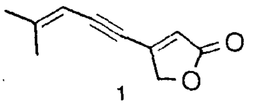
the quite recently reported first synthesis of this natural product, which involves a Pd-catalysed cross-coupling reaction between 4-tributylstannylfuran-2(5*H*)-one **3** and 1-iodo-4-methylpent-3-ene-1-yne **4**,[4] suffers some serious disadvantages such as the multi-step preparation of compound **3**, the instability of compound **4** as well as the modest yield of the Pd-catalysed cross-coupling reaction.



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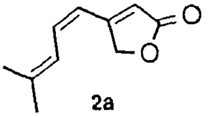

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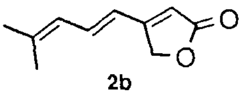

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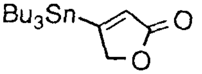

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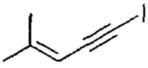


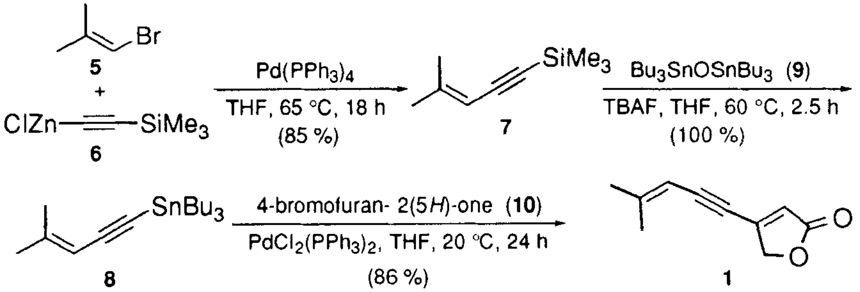
4

We here report a novel and concise synthesis of cleviolide **1**, which allows to prepare efficiently and on a gram scale this naturally-occurring furan-2(5*H*)-one derivative.

As shown in the Scheme, the short reaction sequence which was used to prepare cleviolide **1** commenced with the reaction between commercially available 1-bromo-2-methylpropene **5** and a THF solution of trimethylsilylethynylzinc chloride **6** at 65 °C for 18 h, in the presence of 5 mol % $Pd(PPh_3)_4$, which furnished chemically pure compound **7** in 85 % yield. Compound **7** was then directly converted into 4-methyl-1-tributylstannylpent-3-en-1-yne **8** by a catalytic method for the conversion of 1-alkynylsilanes, allyl- or benzyltrimethylsilane into the corresponding 1-tributylstannanes.[6] In particular, a mixture of 0.5 equiv. of bis(tributyltin) oxide **9** and 1.12 equiv. of compound **7** in dry THF was treated with 0.02 equiv. of tetrabutylammonium fluoride (TBAF) and the resulting mixture was heated to 65 ° C for 2.5 h. The volatiles, *i.e.* THF, the molar excess of **7** and bis(trimethylsilyl) oxide, which was formed in the reaction, were then removed *in vacuo* to give in crude quantitative yield the required organotin derivative **8** having chemical purity higher than 97 %. Finally, according to a modification of the procedure developed by Hoffmann *et al.* for the preparation of 4-(1-alkynyl)furan-2(5*H*)-ones,[7] 4-bromofuran-2(5*H*)-one **10**, which was prepared in 75 % yield by treatment of tetronic acid with 1.2 equiv. of oxalyl bromide and

1.3 equiv. of DMF in CH_2Cl_2,[8] was reacted with 1.2 equiv. of crude compound **8** in THF at room temperature for 24 h, in the presence of 3 mol % $PdCl_2(PPh_3)_2$.

SCHEME



This reaction, which was carried out on a gram scale, delivered 98 % chemically pure cleviolide **1** in 86 % yield after purification of the crude reaction product by MPLC on silica gel. The physical and spectral properties of compound **1**, which was recrystallized from hexane, proved to be in good agreement with those reported by Hollingworth *et al.*[4a]

In conclusion, cleviolide **1** has been efficiently synthesised on a gram scale by a novel convergent approach, which involves the extension to a 1-trimethylsilyl-3-en-1-yne of the one-step direct conversion of 1-trimethylsilyl-1-ynes into the corresponding 1-tributylstannanes. This route to cleviolide is clearly a significant improvement, in terms of efficiency and simplicity, over the procedure previously reported in the literature.[4]

EXPERIMENTAL

GLC analyses were performed on a Dani 6500 gas-chromatograph with a PTV injector equipped with a Dani data station 86.01. Two types of capillary columns were used: a SE-30 bonded FSOT column (30 m x 0.25 mm i.d.) and an AT-Wax bonded FSOT column (30 m x 0.25 mm i.d.). Purifications by MPLC were performed on a Büchi 681 instrument, using a Bischoff 8100 differential refractometer as detector. GLC/MS analyses were performed using a a Q-mass 910 spectrometer interfaced with a Perkin-Elmer 8500 gas-chromatograph. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Gemini 200 MHz spectrometer using TMS as an internal standard. IR spectra were recorded on a Perkin-Elmer 1725-X FT-IR instrument. The following compounds were prepared according to the literature: 4-bromofuran-2(5*H*)-one **10**[8], $Pd(PPh_3)_4$[9], $PdCl_2(PPh_3)_2$.[10]

4-Methyl-1-trimethylsilylpent-3-en-1-yne 7

Trimethylsilylacetylene (17.46 g, 177.77 mmol) was added dropwise to a 0.712 M THF solution of ethylmagnesium bromide (250 ml) which was stirred at 20 °C under a nitrogen atmosphere. After the addition was complete, the mixture was maintained under reflux for 1 h. It was then cooled to 20 °C and added to an ice-cold solution of dry $ZnCl_2$ (31.50 g, 231.12 mmol) in THF (200 ml) and the resulting mixture was stirred under a nitrogen atmosphere at 0 ° C for 0.5 h. A deareated solution of 1-bromo-2-methylpropene **5** (19.11 g, 141.54 mmol) and $Pd(PPh_3)_4$ (8.18 g, 7.08 mmol) in THF (100 ml), which was prepared immediately prior to use, was added to this reaction mixture maintained at 0 °C under stirring. The resulting mixture was allowed to warm up to 20 °C and then it was refluxed for 18 h. After this period, the now yellow suspension was cooled to 20 °C, poured into a large excess of a saturated aqueous NH_4Cl solution and extracted repeatedly with Et_2O. The collected organic extracts were washed with water, dried, filtered over Celite and concentrated at 760 Torr through a Vigreux column. After removal of Et_2O, the residue was concentrated further on at 300 Torr. Pentane (400 ml) was then added and the resulting mixture was filtered over Celite. The filtrate was concentrated at 760 Torr through a Vigreux column and the residue was fractionally distilled to give pure 4-methyl-1-trimethylsilylpent-3-en-1-yne 7 as a clear colourless liquid (18.17 g, 85 % yield): b.p. 72-73 °C/31 Torr. MS, *m/z* (%): 152 (M^+, 22), 137 (100), 109 (11), 97 (9), 83 (18), 59 (13). IR (neat): ν_{max} 2961, 2154, 1626, 1250, 1110, 844, 760 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 5.29 (1 H, s, CH), 1.91 (3 H, s, CH_3), 1.80 (3 H, s, CH_3), 0.19 ppm (9 H, s, $SiMe_3$). Anal. Calcd for $C_9H_{16}Si$: C, 70.97; H, 10.59. Found: C, 71.06; H, 10.71.

4-Methyl-1-tributylstannylpent-3-en-1-yne 8

A flame-dried reaction vessel, which was maintained under an argon atmosphere, was charged with a deareated solution of 4-methyl-1-trimethylsilylpent-3-en-1-yne **7** (3.80 g, 24.95 mmol) in THF (60 ml) and bis(tributyltin) oxide **10** (6.96 g, 11.67 mmol). A 1 M THF solution of TBAF (0.50 ml, 0.50 mmol) was added and the mixture was magnetically stirred at 60 °C for 2.5 h, at which time the volatiles were removed *in vacuo* to give 4-methyl-1-tributylstannylpent-3-en-1-yne **8** as a clear colourless liquid (8.60 g, 100 % yield). MS, *m/z* (%): 313 (54), 311 (44), 257 (37), 255 (32), 201 (57), 199 (100), 121 (47), 119 (38). ^{1}H NMR ($CDCl_3$): δ 5.32 (1 H, s, CH), 1.92 (3 H, s, CH_3), 1.78 (3 H, s, CH_3), 1.62 - 0.81 ppm (27 H, m, C_4H_9). GLC and TLC analyses showed that compound **8** had chemical purity higher than 97 %. This crude compound was used in the next step without any further purification and characterization.

Cleviolide [4-(4'methylpent-3'-en-1'-ynyl)furan-2(5H)-one] 1

A flame-dried reaction vessel, which was maintained under an argon atmosphere, was charged with 4-bromofuran-2(5*H*)-one **10**[7] (3.39 g, 20.83 mmol), $PdCl_2(PPh_3)_2$ (0.44 g, 0.62 mmol) and deareated THF (90 ml) and the mixture was stirred. A deareated solution of compound **8** (8.60 g, 23.29 mmol) in THF (30 ml) was then added and the resulting mixture was stirred at 20 °C for 24 h. The red coloured reaction mixture was poured into a large excess of a saturated aqueous NH_4Cl solution and extracted repeatedly with Et_2O. The collected organic extracts were washed with water and concentrated *in vacuo*. The residue was diluted with Et_2O (200 ml) and stirred at 20 °C with an aqueous 8 M solution of KF (100 ml) for 3.5 h. The mixture was then diluted with Et_2O (100 ml), filtered over Celite and the filtrate was extracted with Et_2O (2 x 50 ml). The collected organic extracts were washed with water, dried and concentrated *in vacuo*. The residue (4.40 g) was dissolved in a mixture of CH_2Cl_2 and hexane (50 ml, 70 : 30) and filtered. The filtrate was concentrated *in vacuo* and the residue was purified by MPLC on silica gel 60 (0.040-0.063 mm), using a mixture of CH_2Cl_2 and hexane (70 : 30) as eluent, to give 98 % pure cleviolide **1** as a pale yellow solid (2.90 g, 86 % yield). This product was recrystallized from hexane to give chemically pure cleviolide as colourless crystals (2.60 g, 77 % yield): m.p. 62-63 °C (from hexane). [Lit.[4a] 63.5 ° C]. MS, *m/z* (%): 162 (68), 133 (9), 104 (100), 89 (8), 78 (27), 63 (20). IR (KBr): ν_{max} 2188, 1774, 1737, 1593, 1300, 1145, 1037, 852 cm^{-1}. ^1H NMR ($CDCl_3$): δ 6.11 (1 H, t, J = 1.90 Hz, H-3), 5.50 (1 H, br s, H-3'), 4.82 (2 H, d, J = 1.90 Hz, H-5), 1.96 (3 H, s, CH_3), 1.92 ppm (3 H, s, CH_3). ^{13}C NMR ($CDCl_3$): δ 173.5 (C), 155.1 (C), 147.7 (C), 120.3 (CH), 104.0 (CH), 103.9 (C), 81.6 (C), 72.9 (CH_2), 25.2 (CH_3), 21.5 ppm (CH_3).

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accepted 02-11-99