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Furanolate-Based Strategy for Sequential 2,3,4-Trisubstitution of Butenolide: Total Synthesis of Nostoclides I and II

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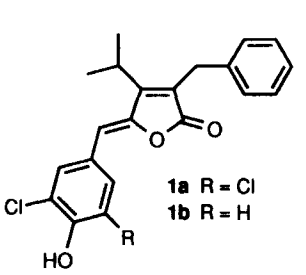
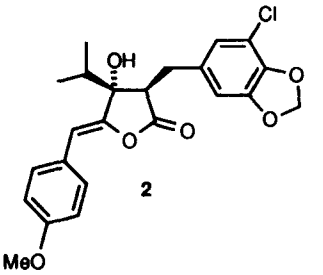
Abstract: The first synthesis of nostoclide I (**1a**) and II (**1b**) has been accomplished in a concise, fully regio- and stereocontrolled manner by sequential 2,3,4-trisubstitution of butenolide (**6**) using 2-furanolates as key intermediates.

Reported in 1993 by Shimizu and co-workers,[2] nostoclides I (**1a**) and II (**1b**) are a pair of cytotoxic lactones produced by a cyanobacterium or blue-green alga (*Nostoc* sp.) from the lichen *Peltigera canina*. Whilst their biological properties are still under investigation, it has been suggested that these compounds may be allelopathic agents since the organism was observed to sustain an unusually clean, contamination-free culture.[2] This proposal is reinforced by the structural resemblance of nostoclides to cyanobacterin (**2**), a metabolite of the freshwater cyanobacterium *S. hofmanni*,[3] which is highly toxic towards other bacteria and green algae.[3a,d] Notwithstanding the novel, densely substituted structures of these natural products and their potential utility as herbicides,[4] synthetic accomplishments in this area have been sparse so far.[5]



1a R = Cl
1b R = H



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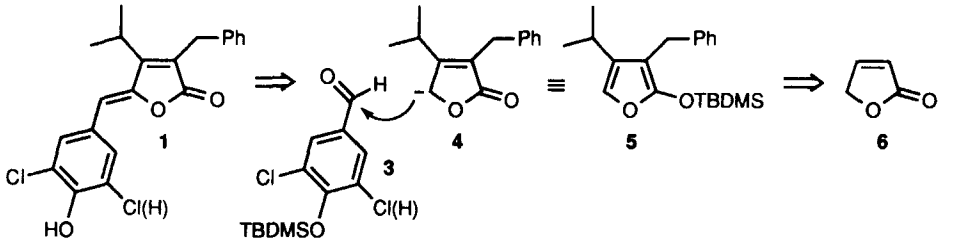
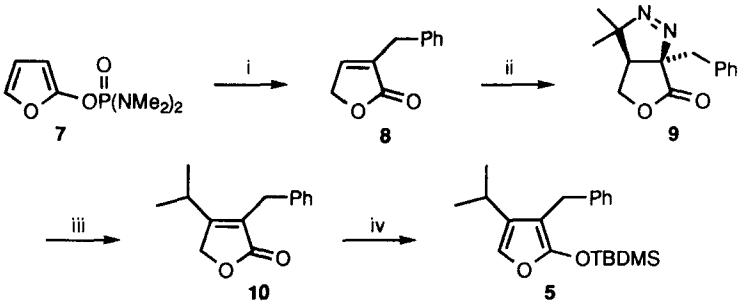
Pursuant to our interest in exploiting the chemistry of 2-furanolates for facile access to functionalized oxacycles,[6,7] we now report the first synthesis of nostoclide I (**1a**) and II (**1b**) which illustrates an innately versatile protocol for constructing 2,3-disubstituted 4-ylidenebutenolides by means of furanolate technology. The strategy we have opted to follow is retrosynthetically presented in Scheme 1. Siloxyfuran **5** was viewed as a stable reagent for synthon **4** and also as a key building block from which both nostoclides could be derived by aldol condensation with the appropriate aldehyde (**3**). It was projected that **5** would be produced in turn from butenolide (**6**) by sequential attachment of the two ring substituents and subsequent silylation.

Scheme 1



The reduction of this plan to practice began with the commercially available 2-furyl N,N,N',N'-tetramethyldiamidophosphate (**7**) which can also be easily prepared in 50-gram batches from butenolide (**6**).[8] Using Näsman's fully documented procedure,[8] furanolate **7** was transformed into 2-benzyl-2-butenolide (**8**)[9] by directed *ortho*-lithiation and benzylation in 72% yield[10] (Scheme 2). Introduction of an isopropyl group onto **8** was realised with complete C(3)-regioselectivity by 1,3-dipolar cycloaddition[11] with 2-diazopropane[12] and thermolysis of the resulting pyrazolinolactone (**9**). Usefully, this two-step sequence could be performed without purification of the cycloadduct to deliver 2-benzyl-3-isopropyl-2-butenolide (**10**)[10] in a yield of 56% after silica gel chromatography. Silylation of **10** with *t*-butyldimethylsilyl triflate (TBDMSOTf) and triethylamime in CH_2Cl_2 (0 to 25 °C) provided 3-benzyl-2-(*t*-butyldimethylsilyloxy)-4-isopropylfuran (**5**) with 88% efficiency.[10]

Scheme 2

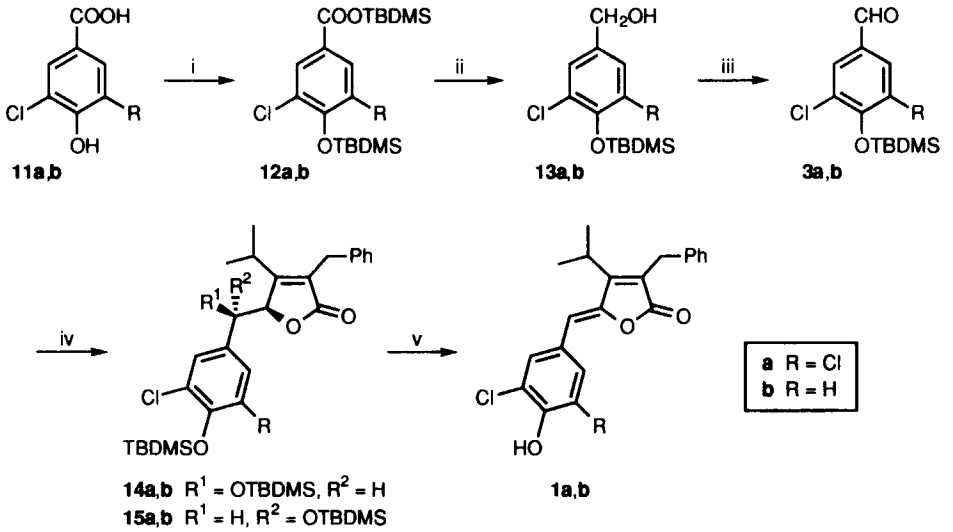


i) *n*-BuLi, THF, -78 °C; $PhCH_2Br$; HCOOH (72%). ii) $Me_2C=\overset{+}{N}=\overset{-}{N}$, Et_2O, 0 °C, 24 h. iii) C_6H_6, reflux, 1 h (56% from **8**). iv) TBDMSOTf (1.1 equiv), Et_3N (1.4 equiv), CH_2Cl_2, 0→25 °C, 24 h (88%).

Having secured furan **5**, the requisite aldehydes **3a** and **3b** were conventionally prepared from the commercial acids **11a** and **11b** by silylation, reduction and Swern oxidation in overall yields of 60 and 44% (Scheme 3).[10,13] Proceeding with our plan, the aldol reaction of aldehyde **3a** with **5** was then addressed. By using boron trifluoride etherate as a catalyst,[6] the *threo* and *erythro* adducts **14a** and **15a** along with nearly equal amounts of the desilylated alcohols (**14a**, R^1=OH; **15a**, R^2=OH) were obtained in a combined yield of 90%.[14] To simplify matters, boron trifluoride etherate was replaced by *t*-butyldimethylsilyl triflate in anticipation that aldolisation would proceed with concurrent full transfer of the silyl group from **5** to the adduct.

Indeed, reaction of **3a** with **5** (1.1 equiv) in the presence of TBDMSOTf (0.5 equiv) in CH_2Cl_2 at -78 °C for 2.5 h followed by quenching with brine afforded exclusively **14a** and **15a** (ratio 2.7:1) in 93% yield. Well aware of the excellent prospects for arrival at **1a** from either of the two diastereoisomers by means of *cis*-selective E1cb elimination,[15] the so obtained mixture of **14a** and **15a** was treated with an excess of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in $CHCl_3$ at 65-70 °C for 24 h. Subsequent quenching with aqueous 3M HCl at 25 °C led uniquely to nostoclide I (**1a**) in 96% yield. Likewise, nostoclide II (**1b**) was produced in two steps (82% overall yield) from furan **5** and aldehyde **3b** by TBDMSOTf-induced aldolisation and subsequent β-elimination of the resulting mixture of diastereoisomers **14b** and **15b** (4.3:1).[10] The synthetic nostoclides **1a** (m.p. 185-187 °C) and **1b** (m.p. 132-133 °C) exhibited spectroscopic properties (^1H and ^{13}C NMR; CD_2Cl_2) in full accord with those reported for the natural samples.[2]

Scheme 3



i) TBDMSCl (2.1 equiv), Et_3N (2.2 equiv), DMAP (0.05 equiv), THF, 0 °C, 0.5 h (**12a** 93%, **12b** 65%). ii) DIBALH (2.2 equiv), Et_2O, 25 °C, 0.5 h (**13a** 87%, **13b** 99%). iii) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -60→25 °C (**3a** 74%, **3b** 68%). iv) **5** (1.1 equiv), TBDMSOTf (0.5 equiv), CH_2Cl_2, -78 °C, 2 h (**14a/15a** 93%, **14b/15b** 91%). v) DBU (4 equiv), $CHCl_3$, reflux, 18-24 h; aq. 3M HCl, 25 °C (**1a** 96%, **1b** 90%).

This protocol for regio- and stereocontrolled assembly of 2,3-disubstituted 4-ylidenebutenolides, as demonstrated by the first synthesis of nostoclides I and II, offers considerable flexibility and should be amenable to the preparation of other members of this class. Such applications are under study and the results will be reported in due course.

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10. Yields refer to chromatographically isolated products. All compounds were characterized by ^{1}H and ^{13}C NMR (300 and 75 MHz respectively, $CDCl_3$) and by elemental analyses and/or HRMS. Data for some new compounds are provided. **10**: mp 55-56 °C. ^{1}H δ 7.26-7.17 (m, 5H), 4.69 (s, 2H), 3.61 (s, 2H), 3.05 (sept, J=7.0 Hz, 1H), 1.08 (d, J=7.0 Hz, 6H). ^{13}C δ 175.0, 167.0, 138.2, 128.5, 128.3, 126.3, 124.3, 68.7, 29.6, 29.3, 27.2, 20.8. **5**: ^{1}H δ 7.27-7.12 (m, 5H), 6.58 (s, 1H), 3.62 (s, 2H), 2.44 (sept, J=7.2 Hz, 1H), 1.03 (d, J=7.2 Hz, 6H), 0.93 (s, 9H), 0.19 (s, 6H). ^{13}C δ 153.8, 141.2, 133.5, 128.1, 128.0, 126.1, 125.5, 95.1, 28.3, 25.4, 24.6, 22.6, 17.8, –4.5. **3a**: mp 67-68 °C. ^{1}H δ δ 9.81 (s, 1H), 7.79 (s, 2H), 1.05 (s, 9H), 0.33 (s, 6H). ^{13}C δ 188.6, 153.6, 130.4, 130.0, 127.7, 25.7, 18.8, –3.1. **3b**: ^{1}H δ 9.83 (s, 1H), 7.88 (d, J=2.2 Hz, 1H), 7.66 (dd, J=8.2, 2.2 Hz, 1H), 6.98 (d, J=8.2, 1H), 1.03 (s, 9H), 0.27 (s, 6H). ^{13}C δ 189.5, 157.0, 131.7, 130.8, 129.5, 126.7, 120.4, 25.4, 18.2, –4.5. **14b**: mp 93-95 °C (R_f = 0.70, 5:1 hexane/EtOAc) ^{1}H δ 7.30 (d, J=2.1 Hz, 1H), 7.23-7.11 (m, 4H), 6.95 (d, J=7.0 Hz, 2H), 6.84 (d, J=8.3 Hz, 1H), 5.09 (d, J=2.1 Hz, 1H), 5.06 (d, J=2.1 Hz, 1H), 3.62 (s, 2H), 2.47 (sept, J=7.1 Hz, 1H), 1.12 (d, J=7.1 Hz, 3H), 1.04 (s, 9H), 1.01 (d, J=7.1 Hz, 3H), 0.87 (s, 9H), 0.22 (s, 6H), 0.06 & -0.08 (s, 2 x 3H). ^{13}C δ 174.0, 166.0, 151.3, 138.0, 132.7, 128.6, 128.4, 128.0, 127.9, 127.7, 126.2, 125.3, 120.4, 86.1, 74.2, 29.8, 29.7, 27.9, 25.72, 25.67, 21.7, 20.0, 18.3, 18.2, –4.4, –4.8, –5.1. **15b**: (R_f = 0.73, 5:1 hexane/EtOAc) ^{1}H δ 7.35 (d, J=2.1 Hz, 1H), 7.21-7.09 (m, 4H), 6.83 (d, J=7.1 Hz, 2H), 6.79 (d, J=8.4 Hz, 1H), 5.06 (d, J=3.0 Hz, 1H), 4.95 (d, J=3.0 Hz, 1H), 3.62 (d, J=15.6 Hz, 1H), 3.55 (d, J=15.6 Hz, 1H), 3.10 (sept, J=6.9 Hz, 1H), 1.17 (d, J=6.9 Hz, 3H), 1.15 (d, J=6.9 Hz, 3H), 1.05 & 0.88 (s, 2x9H), 0.22 (s, 6H), 0.06 & -0.13 (s, 2x3H). ^{13}C δ 173.9, 166.8, 151.4, 138.1, 132.8, 128.6, 128.4, 127.9, 127.2, 126.4, 126.1, 125.4, 120.2, 83.9, 73.6, 29.7, 28.0, 25.74, 25.65, 22.0, 20.0, 18.4, -4.3, -4.4, -4.6, -5.1.
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13. Alternatively, aldehyde **3b** was obtained directly from silyl ester **12b** by reduction under milder conditions (1.26 equiv. DIBALH, Et_2O, -78 °C, 0.5 h) in a persistently moderate yield of 50-51%.
14. The *threo* adducts were distinguished from their *erythro* isomers by the downfield ^{13}C and ^{1}H chemical shifts of the butenolide C-4 and its proton. As a rule, Lewis acid-induced aldol and related reactions of 2-trialkylsiloxyfurans are *threo*-selective (*cf.* ref. 6 & Martin, S.F.; Corbett, J.W. *Synthesis* **1992**, 55-57).
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