Ascidiatrienolide A is a 10-Membered Lactone

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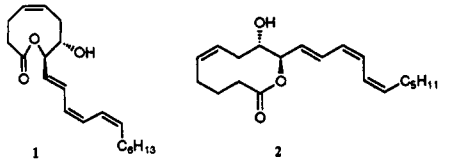
In 1989, Fenical and Lindquist reported the isolation of the ascidiatrienolides from the marine ascidian *Didemnum candidum*, crude extracts from which exhibited strong *in vitro* inhibitory activity toward the enzyme phospholipase A_2.[1] The assigned structures for the ascidiatrienolides are very unusual, being a rare example of eicosanoids[2] that possess an unsaturated nine-membered lactone (*e.g.*, ascidiatrienolide A, **1**). In this communication we report the application of a versatile Claisen rearrangement approach to the efficient synthesis of the core nine-membered unsaturated lactone **8** and its subsequent elaboration to **1**. As a result, the structure of ascidiatrienolide A has

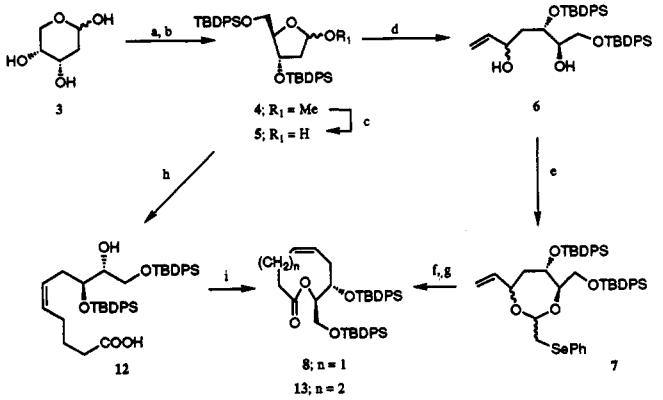


1 **2**

been revised to the ten-membered lactone structure **2** whose synthesis is also described. Construction of the sensitive triene side chain in both targets was achieved using a key Stille coupling reaction.

The cyclization of acyclic precursors to form nine-membered lactones has been applied with varying degrees of success,[3] and ring expansion methods can also be efficient.[4] Scheme I illustrates the Claisen approach to the synthesis of the lactone **8** from 2-deoxy-D-ribose (**3**). Glycosidation in acidic methanol,[5] followed by silylation of the crude methoxy acetal using pyridine and *tert*-butyldiphenylsilyl chloride (TBDPSCl), afforded the bis silyl ether **4** (Scheme I). Demethylation of the furanoside **4** using boron trichloride–dimethyl sulfide complex (BCl_3·Me_2S)[6] gave the required lactol **5**. Treatment of the lactol **5** with vinyl magnesium bromide afforded the 1,4-diol **6** as a 1:1 mixture of diastereo-

Scheme I[a]



[a] (a) HCl, Et_2O, MeOH, 15 min; (b) TBDPSCl, pyridine, room temperature, 30 min (98% from **4**); (c) (i) BCl_3·DMS (1.1 equiv), Et_2O, room temperature, 10 min, (ii) aqueous Na_2CO_3, THF (87–98%); (d) CH_2=$CHMgBr$ (5 equiv), THF, −70 → 0 °C, 2 h (72%); (e) $PhSeCH_2CH(OEt)_2$, PPTS, toluene, heated 1.5 h (98%); (f) $NaIO_4$, $NaHCO_3$, MeOH-CH_2Cl_2-Et_2O-H_2O, room temperature, 2 h; (g) DBU (3 equiv), toluene, heated 16 h (**8**, 85%); (h) $[P^+Ph_3CH_2(CH_2)_3COOH]Br^-$, $NaN(TMS)_2$, toluene, THF, 0 → −70 °C and then **5**, −70 → 0 °C (95%); (i) Yamaguchi lactonization[18] (**13**, 96%).

isomers which were converted[7] into the dioxepane **7** as a mixture of three diastereoisomers. The ring expansion of **7** to the nine-membered lactone **8** was effected by Claisen rearrangement of the intermediate ketene acetal generated by selenoxide elimination.[4,8] The lactone **8** was thus prepared in 58% overall yield from 2-deoxy-D-ribose (**3**).

Deprotection without ring enlargement by transacylation was achieved by treatment of the silyl ether **8** with buffered pyridinium hydrofluoride[9] to afford the alcohol **9** in good yield (Scheme II). Swern oxidation followed by Wittig reaction with 1-formyl-(methylidene)triphenylphosphorane[10] furnished the (*E*)-α,β-unsaturated aldehyde **10** in excellent yield.[11] This was followed by a Wittig homologation[13] in the presence of hexamethylphosphoric triamide (HMPA) to give the separable (*E*,*Z*)- and (*E*,*E*)-dienes **11** as a 5:1 mixture, respectively. The Stille coupling reaction[14] of vinyl iodide **11** with (*Z*)-1-octenyltributylstannane,[15] followed by separation of the resulting mixture of geometrical isomers by HPLC and deprotection of the silyl ether with tetra-*n*-butylammonium fluoride (TBAF), afforded the pure target molecule **1**. The lack of stereocontrol in the Stille coupling could

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(9) Attempted selective deprotection of lactone **8** using tetra-*n*-butylammonium fluoride (TBAF) in tetrahydrofuran (THF), even at low temperatures, removed both silyl groups and caused translactonization to a ten-membered lactone. Pyridinium hydrofluoride was prepared according to the method of Evans, D. A.; Kaldor, S. W.; Jones, T. K.; Clardy, J.; Stout, T. J. *J. Am. Chem. Soc.* **1990**, *112*, 7001–7031.
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(11) Our initial strategy for generating the triene side chain called for a coupling of a (*E*)-vinyl iodide with a dienylcopper reagent from the double carbocupration[12] of acetylene, but we experienced difficulty in generating the required copper reagent.
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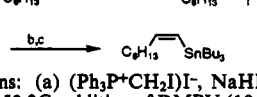
(15) The vinyl stannane was prepared from commercially available heptanal as follows:



Reagents and conditions: (a) $(Ph_3P^+CH_2I)I^-$, NaHMDS, 1 min at room temperature and then −50 °C, addition of DMPU (10 equiv), −50 → −90 °C and then addition of heptanal, 5 min at −90 °C and then room temperature (73%); (b) *t*-BuLi, ether, −78 °C; (c) Bu_3SnCl, −78 °C → room temperature (96%).

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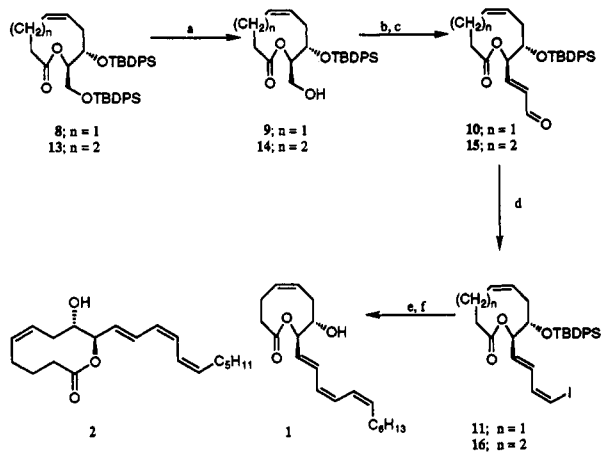
Scheme II[a]



[a] (a) HF–pyridine, pyridine–THF (**9**, 84%; **14**, 85%); (b) dimethyl sulfoxide (DMSO), oxalyl chloride, –78 °C and then Et_3N, –78 °C to room temperature; (c) $Ph_3P{=}CHCHO$, CH_2Cl_2, room temperature, 16 h (**10**, 83%; **15**, 77%); (d) (i) $(Ph_3P^+CH_2I)I^-$, NaHMDS, 1 min at room temperature then –50 °C, addition of HMPA (5 equiv) for **11** or addition of 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU; 10 equiv) for **16**, –50 → –90 °C then addition of aldehyde, 5 min –90 °C then room temperature [**11**, 96% of 5:1 mixture of (*E*,*Z*)-:(*E*,*E*)-dienyl iodides; **16**, 91% of 4:1 mixture of (*E*,*Z*)-:(*E*,*E*)-dienyl iodides], (ii) HPLC separation; (e) $C_6H_{13}CH{=}CHSnBu_3$, $Pd(MeCN)_2Cl_2$ (catalyst), DMF, room temperature, 144 h [63%; comprising 33% (*E*,*Z*,*Z*)-triene (precursor to **1**) and 30% (*E*,*Z*,*E*)-triene separated by HPLC] or C_5H_{11}-$CH{=}CHSnBu_3$, $Pd(MeCN)_2Cl_2$ catalyst, DMF, room temperature, 48 h; (f) TBAF, THF, (**1**, 72%; **2**, 48% from **16**).

not be overcome even after extensive variation of solvent, catalyst, vinyl metal, and halide.[16]

The spectroscopic and physical properties of the synthetic material **1** were found to differ from those of ascidiatrienolide A.[17] In particular, the natural product contained two multiplets at *ca.* δ 1.7 (2H) and 2.6 (1H), which were absent in the ^1H NMR spectrum of **1**, and the two *C*H–O signals deviated by more than 3 ppm in the ^{13}C NMR spectrum. Significantly, the peak at *m*/*z* 162 in the EI mass spectrum of the natural product, which Lindquist and Fenical had interpreted as a $C_{12}H_{19}$ side chain, was absent from the EI mass spectrum of **1**. In revising the structure, we could reposition a side-chain methylene group between the ring double bond and lactone carbonyl groups, leading to a 10-membered lactone (**2**) carrying a $C_{11}H_{17}$ side chain. Disconnection of structure **2** leads again to 2-deoxy-D-ribose, and the synthesis is illustrated in Schemes I and II. Wittig reaction of the lactol **5** with the ylide derived from (4-carboxybutyl)-triphenylphosphonium bromide afforded the (*Z*)-olefinic acid **12** in excellent yield (Scheme I). Lactonization[18] of the acid **12** gave the 10-membered lactone **13** in near quantitative yield. Elaboration of the (*E*,*Z*,*Z*)-side chain was carried out using the same methodology as for **1**. Stille coupling[14] of the vinyl iodide **16** with the appropriate stannane[19] followed by *in situ* desilylation gave the target molecule **2**. This Stille coupling occurred with *complete retention of stereochemistry* to give a single triene. This is remarkable when compared with the previous reaction to form **1** in which a mixture of trienes was observed. The synthetic material **2** had spectroscopic properties[20] identical to natural ascidiatrienolide A,[1] but the optical rotation ($[\alpha]^{18}_D$ +77.6, *c* 0.93 in $CHCl_3$) was larger in magnitude and opposite in sign to that of the natural product ($[\alpha]_D$ –14.8, *c* 4.5 in $CHCl_3$), from which we conclude that ascidiatrienolide A is the (8*R*,9*S*) enantiomer. Thus ascidiatrienolide A is proposed to have the same absolute configuration as neodidemnilactone, a side-chain geometrical isomer of **2**, which was recently isolated from a marine tunicate.[21]

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Supplementary Material Available: Details of the experimental procedure and spectroscopic data for compounds **1**, **2**, **5**, **8**, **9**, and **14** (4 pages). Ordering information is given on any current masthead page.

(16) For a related problem in the synthesis of (*E*,*E*,*E*)-trienes, see: Hong, C. Y.; Kishi, Y. *J. Am. Chem. Soc.* **1991**, *113*, 9693–9694.

(17) NMR data for **1**: ^1H (400 MHz, C_6D_6) δ 0.88 (3H, t, *J* = 6.8, CH_3), 1.09–1.36 (9H, m, 4 CH_2, OH), 1.90–2.19 (8H, m, 4 CH_2), 3.51–3.57 (1H, m, C*H*OH), 5.38–5.47 (3H, m, endocyclic =CH, OC*H*CH=, =CHC_6H_{13}), 5.56 (1H, dt overlapping, *J* = 8.5, 10.8, endocyclic =CH), 5.79 (1H, dd, *J* = 6.6, 15.2, OCHC*H*=), 6.00 (1H, dd as t, *J* = 11.1, 11.1, =CH), 6.34 (1H, dd as t, *J* = 11.0, 11.6, =CH), 6.47 (1H, dd as t, *J* = 10.6, 10.6, =CH), 7.00 (1H, dd, *J* = 11.5, 15.2, OCHCH=C*H*); ^{13}C (100 MHz, C_6D_6) δ 14.3 (CH_3), 23.0, 24.1, 27.8, 29.2, 29.9, 32.1, 33.7, 34.0 (CH_2), 75.0, 79.5, 124.1, 126.1, 128.5, 129.3, 131.6, 134.2 (CH), 173.7 (C=O).

(18) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989–1993.

(19) (*Z*)-1-Heptenyltributylstannane was synthesized using the same methodology described in ref 15 starting from commercially available hexanal.

(20) NMR data for **2**: ^1H (250 MHz, C_6D_6) δ 0.89 (3H, t, *J* = 6.7, CH_3), 1.21–1.39 (8H, m, 4 CH_2), 1.62–1.74 (2H, m, CH_2), 1.93–2.00 (2H, m, CH_2), 2.07–2.14 (5H, m, 2 CH_2, OH), 2.58–2.72 (1H, br m, CH_2), 3.60–3.67 (1H, br m, C*H*OH), 5.32–5.49 (3H, m, OC*H*CH=, C_5H_{11}C*H*=, ring CH=), 5.69–5.77 (1H, m, ring CH=), 5.77 (1H, dd, *J* = 7.1, 15.1, OCHC*H*=), 6.04 (1H, dd, *J* = 10.9, 11.0, CH=), 6.37 (1H, dd, *J* = 11.3, 11.5, CH=), 6.52 (1H, dd, *J* = 11.1, 11.8, CH=), 7.11 (1H, dd, *J* = 11.6, 15.1, OCHCH=C*H*); ^{13}C (100 MHz, C_6D_6) δ 14.2 (CH_3), 22.9, 25.5, 26.4, 27.8, 29.5, 31.7, 32.9, 34.9 (CH_2), 72.0, 76.2, 124.0, 125.0, 126.2, 128.3, 129.6, 131.5, 131.8, 134.3 (CH), 172.7 (C).

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