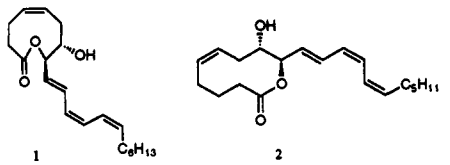
Ascidiatrienolide A is a 10-Membered Lactone

Miles S. Congreve, Andrew B. Holmes,*
Andrew B. Hughes, and Mark G. Looney

University Chemical Laboratory
Lensfield Road, University of Cambridge
Cambridge CB2 1EW, U.K.

Received February 16, 1993

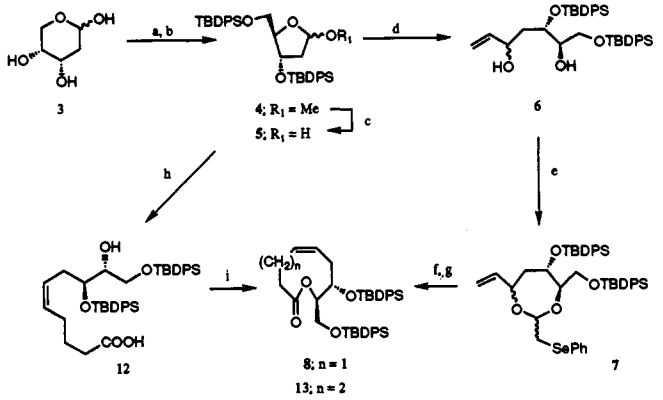
In 1989, Fenical and Lindquist reported the isolation of the ascidiatrienolides from the marine ascidian *Didemnum candidum*, crude extracts from which exhibited strong *in vitro* inhibitory activity toward the enzyme phospholipase A_2.[1] The assigned structures for the ascidiatrienolides are very unusual, 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



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]

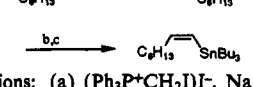


[a] (a) HCl, Et_2O, MeOH, 15 min; (b) TBDPSCl, pyridine, room temperature, 30 min (98% from **4**); (c) (i) BCl_3·DMS (1.1 equiv), Et_2O, room temperature, 10 min, (ii) aqueous Na_2CO_3, THF (87–98%); (d) CH_2=$CHMgBr$ (5 equiv), THF, −70 → 0 °C, 2 h (72%); (e) $PhSeCH_2CH(OEt)_2$, PPTS, toluene, heated 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) [$P^+Ph_3CH_2(CH_2)_3$-COOH]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

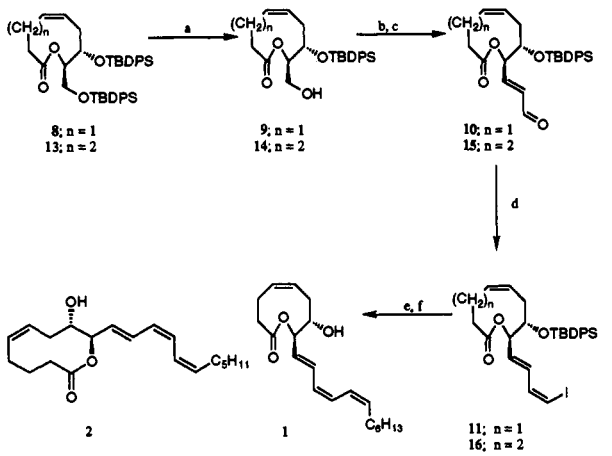
(1) Lindquist, N.; Fenical, W. *Tetrahedron Lett.* **1989**, *30*, 2735–2738.
(2) Kigoshi, H.; Niwa, H.; Yamada, K.; Stout, T. J.; Clardy, J. *Tetrahedron Lett.* **1991**, *32*, 2427–2428.
(3) Illuminati, G.; Mandolini, L. *Acc. Chem. Res.* **1981**, *14*, 95–102. Still, W. C.; Galynker, I. *J. Am. Chem. Soc.* **1982**, *104*, 1774–1776. Funk, R. L.; Abelman, M. M.; Munger, J. D., Jr. *Tetrahedron* **1986**, *42*, 2831–2846. Trost, B. M.; Verhoeven, T. R. *J. Am. Chem. Soc.* **1980**, *102*, 4743–4763. Tabuchi, T.; Kawamura, K.; Inanagu, J.; Yamaguchi, M. *Tetrahedron Lett.* **1986**, *27*, 3889–3890. Wada, M.; Shigehisa, T.; Akiba, K. *Tetrahedron Lett.* **1985**, *26*, 5191–5194. Lygo, B.; O'Connor, N. *Synlett* **1990**, 282–284. Nicolaou, K. C.; McGarry, D. G.; Somers, P. K.; Kim, B. H.; Ogilvie, W. W.; Yiamikouros, G.; Prasad, C. V. C.; Veale, C. A.; Hark, R. R. *J. Am. Chem. Soc.* **1990**, *112*, 6263–6276. Pirrung, F. O. H.; Steeman, W. J. M.; Hiemstra, H.; Speckamp, W. N.; Kaptein, B.; Boesten, W. H. J.; Schoemaker, H. E.; Kamphuis, J. *Tetrahedron Lett.* **1992**, *33*, 5141–5144.
(4) Curtis, N. R.; Holmes, A. B.; Looney, M. G. *Tetrahedron* **1991**, *47*, 7171–7178. Carling, R. W.; Curtis, N. R.; Holmes, A. B. *Tetrahedron Lett.* **1989**, *30*, 6081–6084. Carling, R. W.; Clark, J. S.; Holmes, A. B. *J. Chem. Soc., Perkin Trans 1* **1992**, 83–94. Ochiai, M.; Iwaki, S.; Ukita, T.; Nagao, Y. *Chem. Lett.* **1987**, 133–136. Posner, G. H.; Webb, K. S.; Asirvathan, E.; Jew, S.-S.; Degl'innocenti, A. *J. Am. Chem. Soc.* **1988**, *110*, 4754–4762. Vedejs, E.; Powell, D. W. *J. Am. Chem. Soc.* **1982**, *104*, 2046–2048. Suginome, H.; Yamada, S. *Tetrahedron* **1987**, *43*, 3371–3386. Fouque, E.; Rousseau, G.; Seyden-Penne, J. *J. Org. Chem.* **1990**, *55*, 4807–4817.
(5) Recondo, E. F.; Rinderknecht, H. *Helv. Chim. Acta* **1959**, *42*, 1171–1173. Bochkov, A. F.; Zaikov, G. E. In *Chemistry of the O-Glycosidic Bond*; Schuerch, C., Ed.; Pergamon: Oxford, 1979.
(6) Goff, D. A.; Harris, R. N.; Bottaro, J. C.; Bedford, C. D. *J. Org. Chem.* **1986**, *51*, 4711–4716. Castañeda, A.; Kucera, D. J.; Overman. L. E. *J. Org. Chem.* **1989**, *54*, 5695–5707.
(7) Baudat, R.; Petrzilka, M. *Helv. Chim. Acta* **1979**, *62*, 1406–1410.
(8) Petrzilka, M. *Helv. Chim. Acta* **1978**, *61*, 3075–3078.
(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.
(10) Trippett, S.; Walker, D. M. *J. Chem. Soc.* **1961**, 1266–1272.
(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.
(12) Furber, M.; Taylor, R. J. K. *J. Chem. Soc., Perkin Trans. 1* **1986**, 1809–1815.
(13) Stork, G.; Zhao, K. *Tetrahedron Lett.* **1989**, *30*, 2173–2174.
(14) Stille, J. K.; Simpson, J. H. *J. Am. Chem. Soc.* **1987**, *109*, 2138–2152. Stille, J. K.; Groh, B. L. *J. Am. Chem. Soc.* **1987**, *109*, 813–817.
(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%).

0002-7863/93/1515-5815$04.00/0

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]

Acknowledgment. We thank the Science and Engineering Research Council (U.K.) for supporting this work and Zeneca Agrochemicals (Jealott's Hill), Pfizer Central Research (Sandwich), and Shell Research for generous financial support. We thank Professor W. Fenical for supplying spectra of ascidiatrienolide A and for helpful suggestions and Dr. N. R. Curtis for his interest in this work. The Cambridge spectroscopy section and the SERC Swansea Mass Spectrometry Service are warmly thanked for acquisition of spectroscopic data.

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=, =C*H*C_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).

(21) Niwa, H.; Inagaki, H.; Yamada, K. *Tetrahedron Lett.* **1991**, *32*, 5127–5128.