Synthesis of the Tetrahydropyran Subunit (C8–C20 Fragment) of (–)-Dactylolide and (–)-Zampanolide

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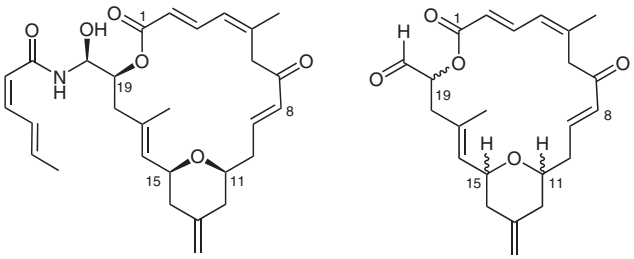
Abstract: The asymmetric synthesis of the tetrahydropyran containing C8–C20 fragment, a common key subunit of both (–)-dactylolide and (–)-zampanolide, is described. The salient feature of this synthesis is the extension of carbon chains using alkynols followed by the use of an alkyne system to generate the desired functionalities, in particular formation of the embedded pyran via an intramolecular oxa-Michael addition of a β-hydroxyynone.

Key words: tetrahydropyran, dactylolide, zampanolide, hydroxyynone, alkyne

(–)-Zampanolide (**1**) and (+)-dactylolide (**2b**, Figure 1) are naturally occurring 20-membered macrolactones isolated in 1996 (by Higa et al.)[1] and 2001 (by Riccio et al.),[2] respectively, from two different marine sponges. Both of these cytotoxic natural products have a structurally unique skeleton which consists of a highly unsaturated 20-membered macrolactone, a 2,6-*cis*-disubstituted 4-exomethylene tetrahydropyran, and two trisubstituted olefins. Compound **1** was shown to exhibit significant cytotoxic activity against a variety of tumor cell lines.[3] It was originally assumed that **1** and **2b** display the same absolute stereochemistry; notably, while **1** was found to be highly potent, **2b** only displayed a modest biological activity. This suggested that the *N*-acyl hemiaminal side chain of **1** is important for its significant cytotoxic activity. However, it was subsequently shown through synthesis of (–)-dactylolide (**2a**) that the enantiomeric relationship is not the same for the natural (–)-zampanolide (**1**) and (+)-dactylolide (**2b**). Interestingly, it could be shown that the potency of (–)-dactylolide (**2a**) in biological assays was on the order of the potency observed for its enantiomer (+)-dactylolide (**2b**) confirming the importance of the *N*-acyl hemiaminal side chain for high potency of **1**.[4] The unusual structures of both the macrolides coupled with the interesting biological profiles makes these compounds prime targets for synthetic studies. The first total synthesis of both these macrolides was achieved by Smith and coworkers providing the relative and absolute stereochemical assignment.[5] Since then, a number of total syntheses[6] and several formal synthesis[7] have appeared in the literature. Our interest in the synthesis of macrolides and tetrahydropyran containing natural products[8] impelled us to pursue the synthesis of the potent cytotoxic compounds (–)-zampanolide (**1**) and (–)-dactylolide (**2a**). Here we report a new synthetic route for the important pyran-containing subunit, the C_8–C_{20} fragment of these natural products.



(–)-zampanolide (**1**)

11*S*,15*S*,19*S*: (–)-dactylolide (**2a**)
11*R*,15*R*,19*R*: (+)-dactylolide (**2b**)

Figure 1 Structure of zampanolide and dactylolide

Our disconnection approach of both (–)-zampanolide (**1**) and (–)-dactylolide (**2a**) is shown in Scheme 1. As demonstrated by Hoye,[6c] **1** can be obtained from **2a** by introduction of *N*-acyl hemiaminal side chain **3**. Further disconnection of **2a** revealed two fragments, an acid fragment **4** and a tetrahydropyran fragment **5**. The latter fragment **5** was envisioned to come from a known compound **6** via hydroxyynone cyclization for the tetrahydropyran ring formation as the key step. The use of alkynols allows for the straightforward carbon-chain extension, and the alkyne provides the necessary functionality for the installation of the tetrahydropyran during the course of the synthesis.

The synthesis began with the known hydroxy Weinreb amide (**6**, Scheme 2) which was obtained in four steps from L-malic acid following a previously reported protocol.[9] Initially, the four-carbon extension was achieved by the addition of homopropargyl benzyl ether (**7**) using ethyl magnesium bromide as a base to Weinreb amide **6**, which gave the desired alkynone **8**. Next, the hydroxyynone **8** was subjected to the key cyclization by the treatment with AgOTf in dichloromethane at room temperature to give the pyranone **9** in 99% yield.[10] Unfortunately, reduction of the double bond and the deprotection of the benzyl ether as a one-pot reaction (10% Pd/C in EtOAc or 10% Pd/C in EtOH) did not provide satisfactory results, **11** was isolated only in less than 20% yield along with the reduced benzyl ether **10**. Therefore, tetrahydropyranone **11** was obtained from compound **9** via a two-step sequence, reduction of double bond to **10** using

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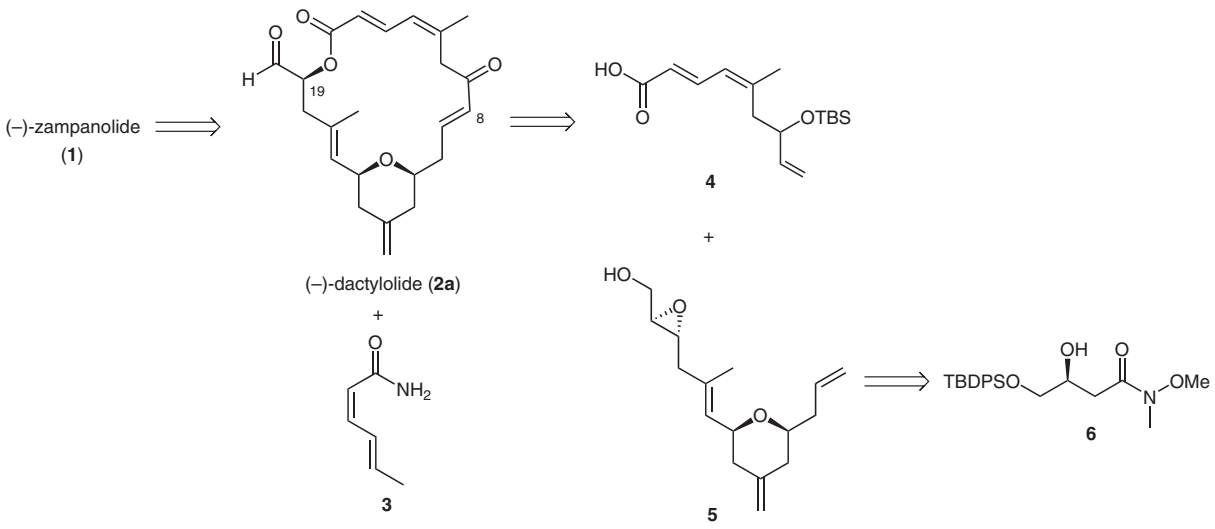
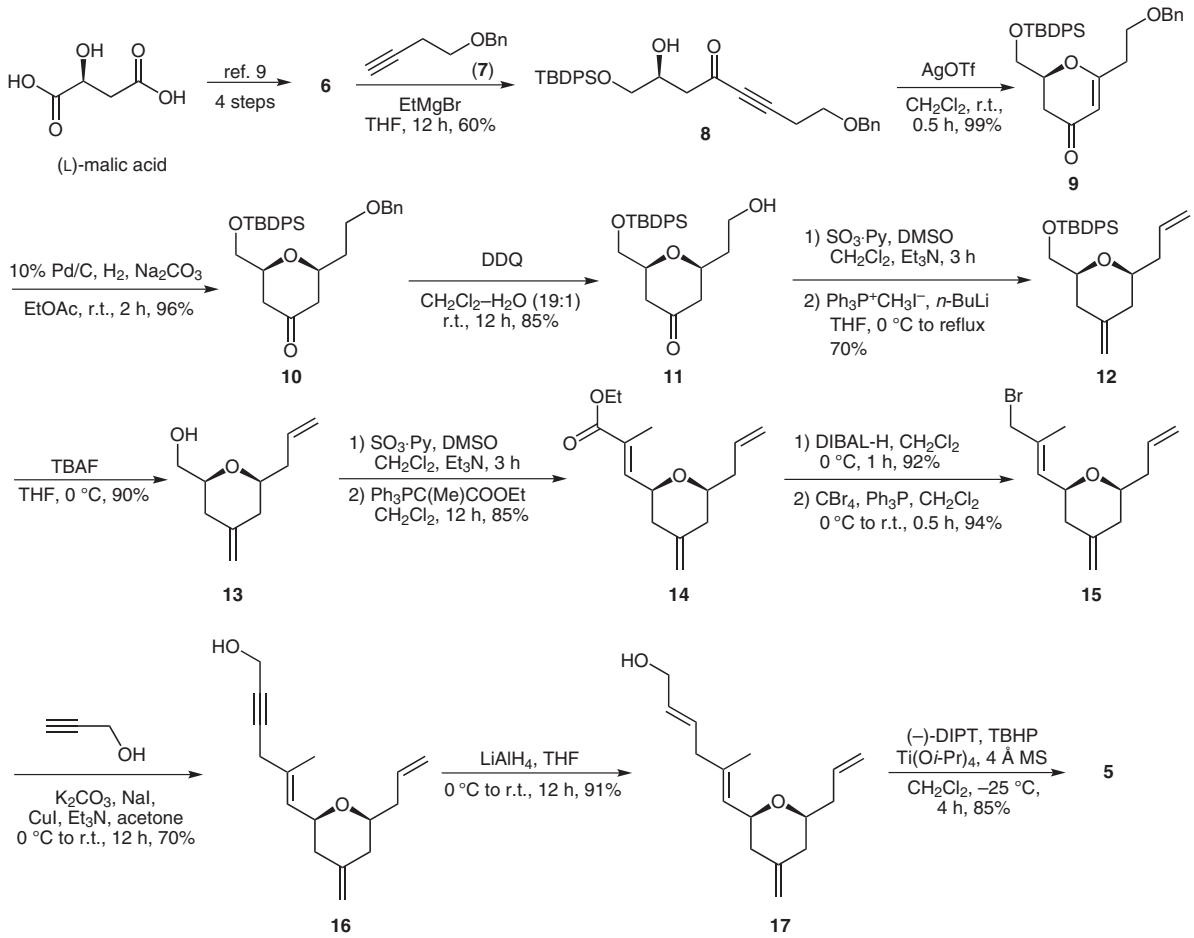


Scheme 1 Retrosynthetic analysis

10% Pd/C and Na_2CO_3 in EtOAc[11] followed by removal of the benzyl ether using DDQ in 81% yield. Oxidation of alcohol **11** using SO_3×py–DMSO (Parikh–Doering oxidation) to the corresponding aldehyde and a subsequent Wittig olefination of both ketone and aldehyde with methyltriphenylphosphonium iodide provided alkene **12**. Desilylation of *tert*-butyldiphenylsilyl ether **12** was accomplished using tetrabutylammonium fluoride to give the alcohol **13** in 92% yield. Oxidation of the alcohol **13** led to an aldehyde, which was extended to the α,β-unsaturated ester by Wittig olefination with Ph_3P=C(Me)COOEt affording **14** in good yield. The next task was chain extension at C_{18} using a three-carbon unit. Reduction of ester **14** with DIBAL-H and subsequent treatment with



Scheme 2 Synthesis of C8–C20 fragment

carbontetrabromide and triphenylphosphine provided the bromide **15** in 86% yield. At this point the three-carbon unit was introduced to compound **15** through a CuI/K_2CO_3/NaI-mediated coupling reaction to give **16** in 70% yield.[12] Reduction of the alkyne functionality to the desired *trans*-olefin by $LiAlH_4$ afforded the allylic alcohol **17** in 91% yield. Finally, Sharpless asymmetric epoxidation of **17** gave target compound **5** in 85% yield. This fragment is Hoye's advanced intermediate in his syntheses of (–)-dactylolide and (–)-zampanolide. Our spectral data were in accordance with the reported data.[6c,13]

In summary, we have demonstrated a concise synthesis of a common tetrahydropyran subunit of (–)-dactylolide and (–)-zampanolide. The tetrahydropyran ring formation was achieved by cyclization of a hydroxyynone which through its simplicity represents a highly efficient strategy which is based on the extension of carbon chains using alkynols followed by the use of the newly introduced alkyne systems to generate the desired functionalities.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

Acknowledgment

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(13) **Spectral Data for Representative Compounds**
(*S*)-8-(Benzyloxy)-1-(*tert*-butyldiphenylsilyloxy)-2-hydroxyoct-5-yn-4-one (8)
$[\alpha]_D^{31}$ –8.5 (*c* 1.0, $CHCl_3$). IR (KBr): ν_{max} = 3442, 2929, 2215, 1670, 1426, 1110, 822, 703 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.65–7.59 (m, 4 H), 7.43–7.21 (m, 11 H), 4.53 (s, 2 H), 4.25–4.16 (m, 1 H), 3.60 (t, *J* = 2.9 Hz, 2 H), 3.60 (td, *J* = 10.9, 5.1 Hz, 2 H), 2.74–2.71 (m, 2 H), 2.65 (t, *J* = 6.5 Hz, 2 H), 2.03 (br s, 1 H), 1.06 (s, 9 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 186.0, 137.6, 135.4, 132.9, 129.8, 128.4, 127.7, 127.6, 91.6, 81.4, 73.0, 68.0, 67.0, 66.8, 48.7, 26.8, 20.4, 19.1. ESI-HRMS: *m/z* calcd for $C_{31}H_{36}NaO_4Si$: 523.2306 $[M + Na]^+$; found: 523.2295.
(2*S*,6*S*)-2-[2-(Benzyloxy)ethyl]-6-[(*tert*-butyldiphenylsilyloxy)methyl]dihydro-2*H*-pyran-4 (3*H*)-one (10)
$[\alpha]_D^{27}$ –10 (*c* 1.0, $CHCl_3$). IR (KBr): ν_{max} = 2928, 2858, 1640, 1463, 1426, 1363, 1111, 701 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.64 (td, *J* = 7.5, 1.3 Hz, 4 H), 7.44–7.17 (m, 11 H), 4.46 (AB, *J* = 12.2 Hz 1 H), 4.41 (AB, *J* = 12.2 Hz, 1 H), 3.83–3.49 (m, 6 H), 2.35 (dd, *J* = 14.1, 4.5 Hz, 3 H), 2.20 (ddd, *J* = 14.1, 11.5, 4.5 Hz, 1 H), 1.95–1.73 (m, 2 H), 1.02 (s, 9 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 207.3, 135.6, 135.5, 133.3, 133.2, 129.6, 128.3, 127.6, 127.5, 77.0, 73.9, 73.0, 66.3, 66.0, 47.7, 44.0, 36.4, 26.7, 19.2. ESI-HRMS: *m/z* calcd for $C_{31}H_{38}NaO_4Si$: 525.2437 $[M + Na]^+$; found: 525.2443.
(*E*)-6-[(2*S*,6*S*)-6-Allyl-4-methylenetetrahydro-2*H*-pyran-2-yl]-5-methylhex-5-en-2-yn-1-ol (16)
$[\alpha]_D^{28}$ –15.3 (*c* 0.5, $CHCl_3$). IR (KBr): ν_{max} = 3458, 2932, 2853, 2325, 1647, 1427, 1219, 1015, 893, 771 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 5.91–5.74 (m, 1 H), 5.48 (dq, *J* = 7.1, 1.1 Hz, 1 H), 5.12–5.08 (m, 1 H), 5.08–5.01 (m, 1 H), 4.71 (t, *J* = 1.5 Hz, 2 H), 4.26 (s, 2 H), 4.00 (ddd, *J* = 10.9, 7.9, 2.8 Hz, 1 H), 3.41–3.30 (m, 1 H), 2.93 (s, 2 H), 2.45–2.32 (m, 1 H), 2.29–2.12 (m, 3 H), 2.06 (t, *J* = 12.8 Hz, 1 H), 1.93 (t, *J* = 12.8 Hz, 1 H), 1.58 (br s, 1 H), 1.75 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 143.8, 134.0, 133.3, 126.4, 116.5, 108.3, 82.6, 80.4, 76.1, 75.1, 50.9, 40.2, 39.4, 29.2, 28.3, 16.4. ESI-HRMS: *m/z* calcd for $C_{16}H_{22}NaO_2$: 269.1512 $[M + Na]^+$; found: 269.151.
[(2*R*,3*R*)-3-{(*E*)-3-[(2*S*,6*S*)-6-Allyl-4-methylenetetrahydro-2*H*-pyran-2-yl]-2-methylallyl}oxiran-2-yl]-methanol (5)
$[\alpha]_D^{27}$ –15.5 (*c* 1.0, CH_2Cl_2). IR (KBr): ν_{max} = 3425, 3074, 2980, 2937, 2896, 1649, 1433 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 5.92–5.70 (m, 1 H), 5.34 (dq, *J* = 7.7, 1.0 Hz, 1 H), 5.14–5.10 (m, 1 H), 5.09–5.02 (m, 1 H), 4.74 (t, *J* = 1.5 Hz, 2 H), 4.04 (ddd, *J* = 10.8, 7.7, 2.6 Hz, 1 H), 3.98–3.88 (m, 1 H), 3.71–3.60 (m, 1 H), 3.43–3.32 (m, 1 H), 3.07 (ddd, *J* = 5.6, 5.6, 2.2 Hz, 1 H), 2.97–2.93 (m, 1 H), 2.41 (dd, *J* = 14.1, 6.2 Hz, 1 H), 2.33 (dd, *J* = 14.5, 6.0 Hz, 1 H), 2.28–2.14 (m, 4 H), 2.05 (t, *J* = 12.6 Hz, 1 H), 1.93 (t, *J* = 12.6 Hz, 1 H), 1.76 (d, *J* = 1.1 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 144.2, 135.0, 134.4, 128.0, 116.9, 108.7, 77.7, 75.4, 61.4, 58.2, 54.5, 41.5, 40.7, 40.6, 39.8, 17.3. ESI-HRMS: *m/z* calcd for $C_{16}H_{24}NaO_3$: 287.1618 $[M + Na]^+$; found: 287.1626.