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Total Syntheses of the Assigned Structures of Lituarines B and C

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The lituarines A−C comprise an architecturally novel, biologically active family of marine natural products (**1**−**3**; Figure 1) reported by Vidal and co-workers in 1992.[1a] Isolated from the sea pen *Lituaria australasaie*, endemic to the western region of the New Caledonian Lagoon near the Baie de St. Vincent, their structures, including the connectivities and relative stereochemistries, were assigned on the basis of multidimensional NMR techniques;[1b] the absolute stereochemistry remains undefined. From the biomedical perspective, the lituarines display significant cytotoxicities toward KB cells [(**1**): IC_{50} = 5.5−7.5 nM; (**2**): IC_{50} = 1−3 nM; (**3**): IC_{50} = 7−9 nM]. Intrigued both by the architecture and the biological activities of the lituarines, we initiated a research program directed toward the total synthesis of the lituarines.[2,3] The Robertson laboratory has also reported progress in this area.[4]

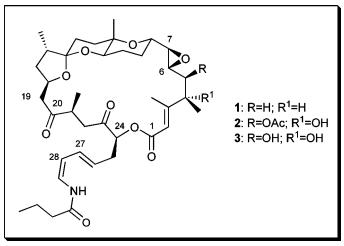
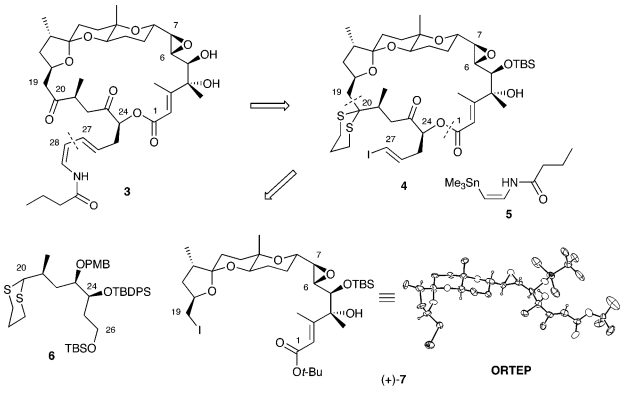


Figure 1. Lituarines A−C.

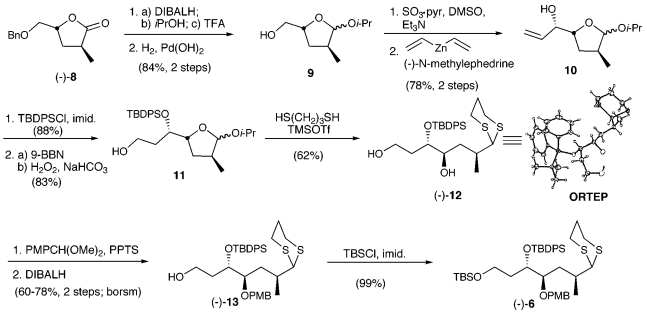
To maximize convergency, we envisioned a synthesis exploiting fragment union between dithiane **6** and advanced alkyl iodide (+)-**7**,[2,3] followed by macrolactonization and late stage introduction of the C(26−33) (*E*,*Z*)-dienamide side chain employing *cis*-vinyl stannane **5** (Scheme 1).

Scheme 1. Retrosynthetic Scheme



After development of a viable route to iodide (+)-**7**,[2,3] the structure was confirmed by X-ray analysis.[5] Our attention thus turned toward the synthesis of dithiane **6** (Scheme 2). Reduction of known lactone (−)-**8**[6] to the corresponding lactol, followed by

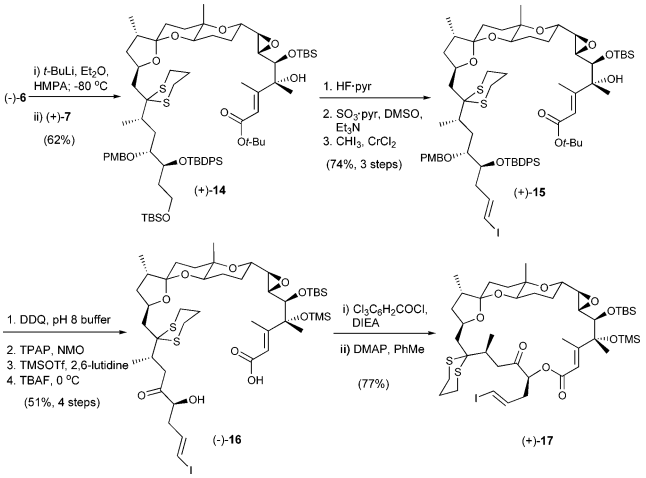
Scheme 2. Synthesis of C(20−26) Dithiane (−)-**6**



hydrogenation, delivered alcohol **9** as a mixture (1:1) of diastereomers. A two-step sequence involving oxidation of the primary alcohol and diastereoselective addition of vinyl zinc[7] to the resulting aldehyde provided allylic alcohol **10**. Silyl protection followed by hydroboration of the terminal olefin then yielded **11**, which in turn was subjected to TMSOTf-mediated dithiane formation to furnish dithiane (−)-**12** in moderate overall yield for the three steps (45%). The structure of (−)-**12** was confirmed via X-ray crystallography.[5] Treatment of diol (−)-**12** with *p*-methoxyphenyl dimethylacetal resulted in a seven-membered PMP-acetal, which upon DIBALH reduction led to (−)-**13**. Protection of the terminal hydroxyl as the TBS ether completed construction of dithiane (−)-**6**. The overall yield for this 10-step sequence was 23%.

Fragment union was achieved by lithiation of (−)-**6** in the presence of HMPA (Scheme 3), followed by addition of alkyl iodide (+)-**7** to furnish (+)-**14**; the yield was 62%. With the core skeleton of lituarines B and C in hand, we advanced to the macrocycle without major difficulty. Removal of the terminal TBS group, followed by an oxidation/Takai olefination[8] sequence, furnished vinyl iodide (+)-**15**. Release of the C(23) PMB group (DDQ) then

Scheme 3. Synthesis of C(1−24) Macrolactone (+)-**17**

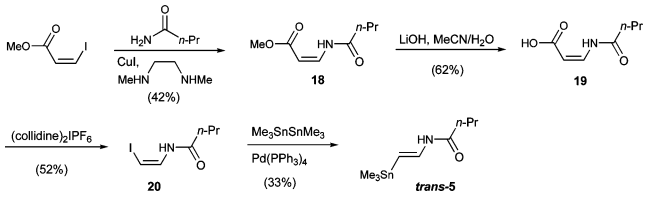


10.1021/ja078293k CCC: $40.75

paved the way for oxidation to the ketone. Subsequent treatment with TMSOTf resulted both in hydrolysis of the *tert*-butyl ester and protection of the C(4) hydroxyl as the TMS ether. A remarkably selective removal of the TBDPS group (TBAF, 0 °C) in the presence of the tertiary TMS and secondary TBS ethers was then achieved. Macrolactonization employing the Yamaguchi conditions[9] completed construction of the desired macrolactone (+)-**17** in good yield (ca. 77%).

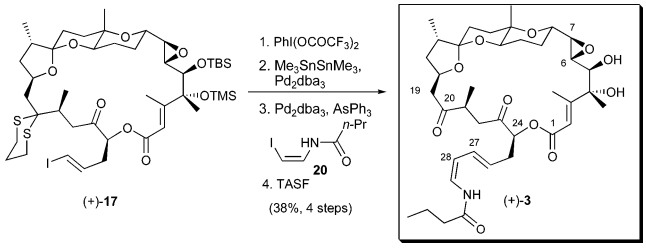
Synthesis of the requisite vinyl stannane (**5**) for installation of the C(26−33) (*E*,*Z*)-dienamide side chain began with known *cis*-2-iodomethylacrylate (Scheme 4);[10] a copper-mediated union[11] with butyramide led to the *cis*-enamide **18**. Hydrolysis of the methyl ester, followed by stereospecific iododecarboxylation,[12] furnished the desired *cis*-iodoenamide **20** as a single isomer. Surprisingly, however, Pd-catalyzed stannylation of **20** resulted in isomerization of the olefin to the *trans* isomer. As a result, we reversed the Stille coupling partners for the side-chain attachment, making use of *cis*-iodoenamide **20**. This tactical revision required preparation of the vinyl stannane from (+)-**17**.

Scheme 4. Synthesis of C(28−33) Enamide Coupling Partner



Toward this end, removal of the dithiane in (+)-**17** employing the Stork protocol[13] was followed by stannylation of the C(27) vinyl iodide moiety (Scheme 5). Stille union with *cis*-iodoenamide **20** resulted in installation of the requisite C(26−33) (*E*,*Z*)-dienamide. Completion of the proposed structure of lituarine C [(+)-**3**] was then achieved by removal of the silicon protecting groups (TASF).[14]

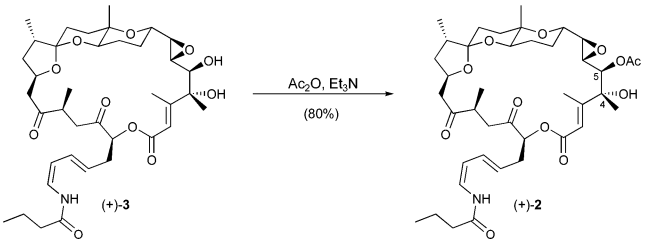
Scheme 5. Completion of Synthesis



With (+)-**3** in hand, we quickly recognized that the spectral properties did not match those of the natural lituarine C.[1,15] Although to date we have been unable to obtain crystals of (+)-**3** suitable for X-ray crystallographic analysis, we do have convincing data to support the structural assignment of (+)-**3**. First, X-ray crystallography confirmed the stereochemical assignments of the C(1−19) tricyclic iodide (+)-**7**,[5] as well as the C(21) and C(24) stereogenicity in (−)-**12**.[5] The geometry of the (*E*,*Z*)-dienamide was assigned by ^{1}H NMR; specifically, the H28−H29 coupling constant (J = 10 Hz) is consistent with a *Z* olefin, while the H26−H27 coupling constant (J = 15 Hz) verifies an *E* olefin.[16] For comparison, the C(26−33) (*E*,*E*)-dienamide corresponding to (+)-**3** was also constructed.[5] In the *E*,*E* congener, the H28−H29 coupling constant (J = 14 Hz) was significantly larger, thereby supporting the *Z* character of the C(28−29) olefin in (+)-**3**. In addition, extensive 2D NMR studies (COSY, TOCSY, NOESY, HMBC, HSQC) of (+)-**3** both confirmed the connectivities and permitted unambiguous assignment of all carbon resonances in the ^{13}C NMR. Finally, no epimerization was observed in any of the transformations after construction of (+)-**14**.

In addition to the synthesis of the proposed structure for lituarine C [(+)-**3**], we also completed the synthesis of the proposed structure of lituarine B (**2**) (Scheme 6). To this end, addition of acetic anhydride to (+)-**3** led chemoselectively to acetylation of the C5 hydroxyl to provide (+)-**2**. As with (+)-**3** and lituarine C, the spectral properties of synthetic (+)-**2** did not match those reported for lituarine B.

Scheme 6. Synthesis of the Proposed Structure of Lituarine B



Taken together, the X-ray crystallographic data, in conjunction with the 1D and 2D NMR studies, permit assignment of the structures of synthetic (+)-**2** and (+)-**3**. Current work is directed toward the determination of the structures of the natural lituarines by synthesis of related diastereomers.

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Supporting Information Available: Experimental procedures and spectroscopic and analytical data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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