Pergamon

Tetrahedron Letters, Vol. 38, No. 36, pp. 6375-6378, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)01467-6

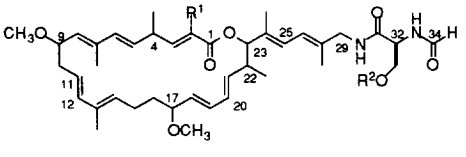
Stereocontrolled Synthesis of the C(1)-C(11) Subunit of the Iejimalides

Matthew T. Mendlik,[a] Muriel Cottard,[a] Tobias Rein,[b]* and Paul Helquist[a]*

[a]Department of Chemistry and Biochemistry, University of Notre Dame, Notre Dame, Indiana 46556 U.S.A.
[b]Department of Organic Chemistry, Technical University of Denmark, DK-2800 Lyngby, Denmark

Abstract: An enantioselective synthesis of the C(1)-C(11) subunit of the iejimalides has been accomplished through a combination of an asymmetric Horner-Wadsworth-Emmons condensation and a chiral pool approach. © 1997 Elsevier Science Ltd.

The iejimalides (**1**) were isolated by Kobayashi, *et al.*, from *Eudistoma* cf. *rigida*, a marine tunicate encountered near Ie Island, Okinawa.[1] The iejimalides are the first macrocyclic lactones found in a tunicate, but these compounds are present in only very low concentrations (A and B in 0.0003% wet weight; C and D in 0.0006% wet weight). They have exhibited potent antitumor activity in mouse leukemia cell lines L1210 (IC_{50} = 0.032 to 10 μg/mL) and L5178Y (IC_{50} = 0.001 to 0.022 μg/mL) and in KB human epidermoid carcinoma cells (IC_{50} = 0.2 to 4.7 μg/mL).[1]



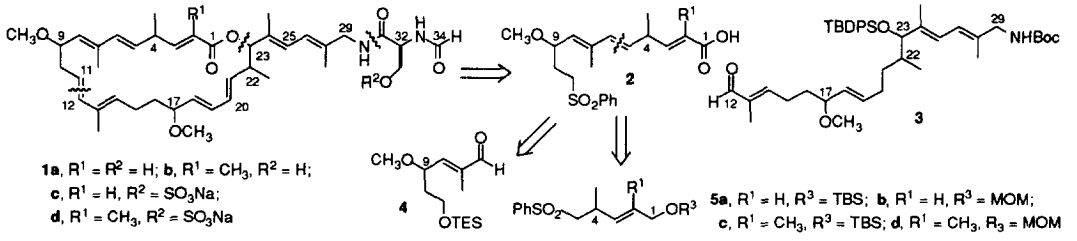
1a, Iejimalide A ($R^1 = R^2 = H$);
1b, Iejimalide B ($R^1 = CH_3$, $R^2 = H$);
1c, Iejimalide C ($R^1 = H$, $R^2 = SO_3Na$);
1d, Iejimalide D ($R^1 = CH_3$, $R^2 = SO_3Na$)

The gross structures of the iejimalides have been determined by NMR studies, but five of their six stereogenic centers remain unassigned. An *anti* relationship at C(22) and C(23) has been assigned tentatively, and the *S* configuration of C(32) has been established due to its presence in an easily characterized serine residue.[1] Thus C(4), C(9), C(17), C(22) and C(23) lack absolute stereochemical assignments. A total synthesis of the iejimalides must therefore permit flexible stereochemical control at these centers to allow the construction of any of the possible diastereomers and enantiomers of **1**. In addition to structural confirmation, the investigation of the total synthesis of the iejimalides has as its goals the production of larger quantities of these compounds as well as the synthesis of selected derivatives. These synthetic materials will be of use in the investigation of the target and mechanism of action of these compounds as potential anticancer agents.

A retrosynthetic analysis of the iejimalides leads to the C(1)-C(11) subunit **2** and the C(12)-C(29) subunit **3** as major precursors (Scheme 1). In previous work, an enantioselective synthesis of the C(17)-C(29) portion of **3** has been achieved in our laboratories through use of asymmetric aldol chemistry and a palladium-catalyzed coupling reaction.[2] In further work, we considered subunit **2** to be potentially available through use of a Julia olefination reaction[3] of **4** and **5**. In turn, we regarded the synthesis of subunit **5** as a good opportunity for the first application in natural products synthesis of one of the types of asymmetric Horner-Wadsworth-Emmons reactions that we have recently developed.[4] At the same time, however, we also wished

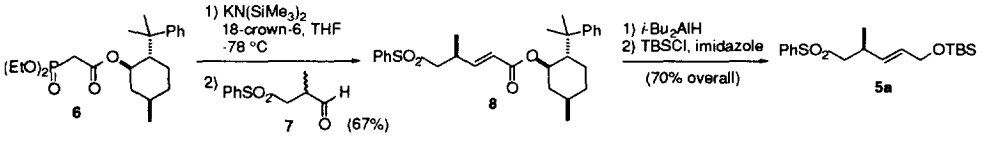
to explore the use of a chiral pool approach as a back-up strategy. This communication reports the successful application of these approaches to the synthesis of an appropriate form of the C(1)-C(11) subunit **2** for use in further structural and synthetic studies of the iejimalides.

Scheme 1



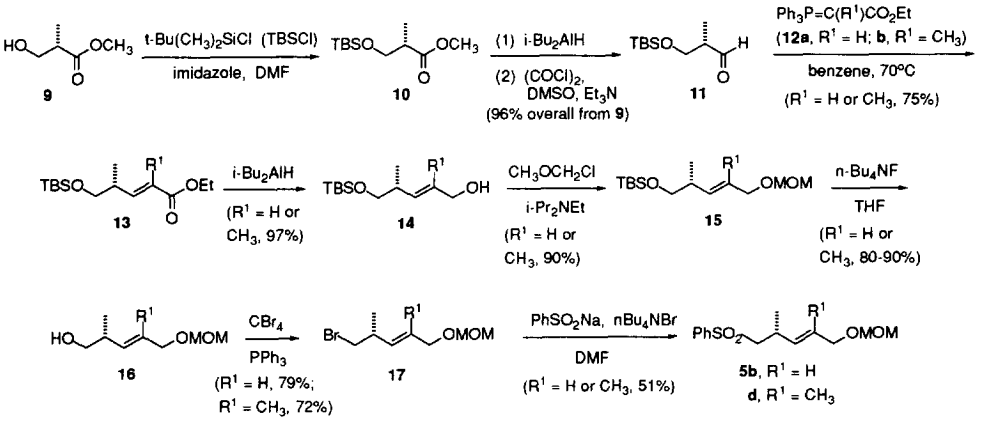
We have obtained the C(1)-C(5) subunit of iejimalides A and C very directly through the condensation of asymmetric Horner-Wadsworth-Emmons reagent **6**[4] with the racemic 3-sulfonyl aldehyde **7**[5] proceeding with kinetic resolution to give unsaturated ester **8** as a 90:10 mixture of diastereomers (Scheme 2).[6] Subsequent reduction of the ester and protection of the alcohol provided unsaturated sulfone **5a** as a C(1)-C(5) subunit for later coupling with the C(6)-C(11) aldehyde **4** (see below).

Scheme 2



We also wished to explore an alternative chiral pool approach to subunits **5** for all of the iejimalides A-D (Scheme 3). The chiral β-hydroxy ester **9** is commercially available in either enantiomerically pure *R* or *S* form, which will provide access to either configuration at C(4) of the iejimalides. Compound **9** was protected as the silyl ether **10** and was then transformed into the aldehyde **11** through the use of a diisobutylaluminum

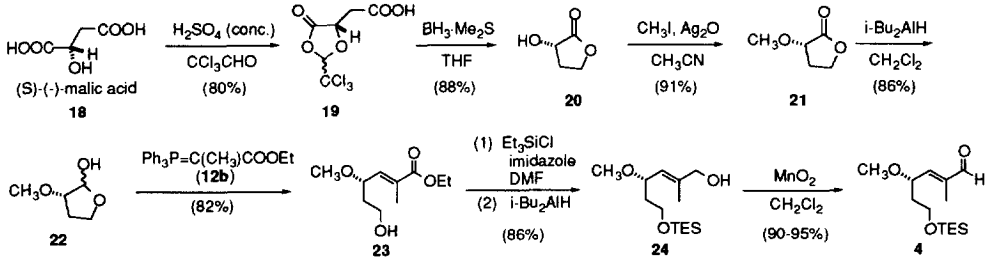
Scheme 3



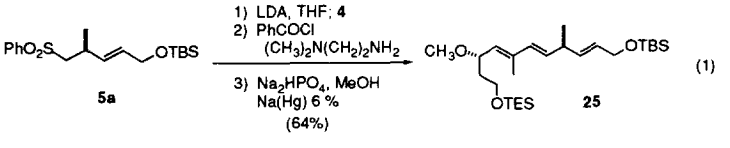
hydride reduction and a subsequent oxidation according to the Swern procedure.[7] The aldehyde was condensed with phosphoranes **12a** and **12b**,[8] followed by reduction of the ester moiety with diisobutylaluminum hydride and protection of the resulting alcohols **14** with chloromethyl methyl ether to obtain protected 1,5-diols **15**.[9] Next the silyl ether was selectively deprotected with tetrabutylammonium fluoride to afford **16**. These alcohols were converted into the bromides **17** followed by transformation into the sulfones **5b** and **5d**.[10]

In principle, an asymmetric Horner-Wadsworth-Emmons reaction should be applicable to the alkene portion of the C(6)-C(11) subunit. However, at the present stage of development of this chemistry, good stereoselectivity is not yet attainable for (*E*)-trisubstituted alkenes. Therefore, a chiral pool approach was developed as an alternative method for synthesis of this fragment (Scheme 4). Malic acid (**18**) is commercially available in either *S* or *R* form, and the selection of either enantiomer allows stereochemical control at C(9) of the iejimalides. Protection of (*S*)-(-)-malic acid was accomplished with chloral through formation of the dioxolanone **19**.[11] Selective reduction of the carboxylic acid moiety in **19** with borane/dimethylsulfide afforded hydroxylactone **20**.[12] Hydroxyl methylation without attendant epimerization was accomplished with CH_3I and Ag_2O.[13] Lactone **21** was then reduced with i-Bu_2AlH to a mixture of lactols **22**.[14] Wittig condensation with phosphorane **12b**[7] afforded α,β-unsaturated ester **23**. The alcohol was protected as the triethylsilyl ether, and the ester was reduced with i-Bu_2AlH to afford **24**. Use of the Swern procedure[7] for the oxidation of **24** to the aldehyde **4** produced some elimination product and gave low yields of the desired product, whereas oxidation with activated MnO_2 provided yields of 90-95%.[15]

Scheme 4



With subunits **4** and **5** in hand, a straightforward coupling could then be accomplished through a Julia olefination[3] of sulfone **5a** (eq 1). The ^1H NMR spectrum of the resulting **25** matches remarkably well the corresponding portions of the spectrum of iejimalide A (**1a**) itself,[1] despite the fact that the separate subunit and the intact natural product are likely to exhibit quite different conformational characteristics. A coupling reaction of **4** with **5b** or **5d** would provide the analogous subunit of iejimalides B and D.



The above routes are highly flexible in providing the necessary choices of configurations at C(4) and C(9), as well as control of the substituent at C(2). The first of the routes to the C(1)-C(5) subunit demonstrates the utility of our recently developed asymmetric Horner-Wadsworth-Emmons reactions.[3] Furthermore, the entire C(1)-C(11) subunit is now available for further studies of the total synthesis, structure, and activity of the iejimalide system. The results of these further studies will be reported in due course.

Acknowledgment. We are grateful to the National Institutes of Health (U.S.A.) and NATO for support

of this work. M.T.M. is pleased to acknowledge a fellowship from Pfizer, Inc., and M.C. acknowledges support provided by a Reilly Fellowship.

Literature References and Footnotes

1. (a) Kobayashi, J.; Cheng, J.; Ohta, T.; Nakamura, H.; Nozoe, S.; Hirata, Y.; Ohizumi, Y.; Sasaki, T. *J. Org. Chem.* **1988**, *53*, 6147-6150. (b) Kikuchi, Y.; Ishibashi, M.; Sasaki, T.; Kobayashi, J. *Tetrahedron Lett.* **1991**, *32*, 797-798.
2. Cottard, M.; Kann, N.; Rein, T.; Åkermark, B.; Helquist, P. *Tetrahedron Lett.* **1995**, *36*, 3115-3118.
3. (a) Kocienski, P. *Phosphorus and Sulfur* **1985**, *24*, 97-127. (b) Hanessian, S.; Ugolini, A.; Dubé, D.; Hodges, P. J.; André, C. *J. Am. Chem. Soc.* **1986**, *108*, 2776-2778. (c) Baker, R.; O'Mahony, M. J.; Swain, C. J. *J. Chem. Soc., Perkin Trans I* **1987**, 1623-1633. (d) Chen, S.-H.; Horvath, R. F.; Joglar, J.; Fisher, M. J.; Danishefsky, S. J. *J. Org. Chem.* **1991**, *56*, 5834-5845. (e) Williams, D. R.; Li, J. *Tetrahedron Lett.* **1994**, *35*, 5113-5116.
4. (a) Rein, T.; Kann, N.; Kreuder, R.; Gangloff, B.; Reiser, O. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 556-558. (b) Rein, T.; Kreuder, R.; von Zezschwitz, P.; Wulff, C.; Reiser, O. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1023-1025. (c) Rein, T.; Anvelt, J.; Soone, A.; Kreuder, R.; Wulff, C.; Reiser, O. *Tetrahedron Lett.* **1995**, *36*, 2303-2306. (d) Rein, T.; Reiser, O. *Acta Chem. Scand.* **1996**, *Ser. B 50*, 369-379. The (*R*)-(+)-pulegone-derived reagent **6** had a stereoisomeric purity of ≥98% based upon ^{1}H NMR.
5. Kraynack, E. A.; Pedersen, S. F. *J. Org. Chem.* **1993**, *58*, 6114-6117.
6. To a solution of phosphonate **6** (0.040 g, 0.10 mmol) and 18-crown-6 (0.117 g, 0.5 mmol) in THF (8 mL) at -78 °C under nitrogen was added $KN(SiMe_3)_2$ (0.18 mL, 0.50 M in toluene, 0.09 mmol). After 30 min, the resulting white slurry was added through a cannula to a precooled solution of aldehyde **7** (0.058 g, 0.30 mmol) in THF (2 mL) at -78 °C. The mixture was stirred at -78 °C for 4 h and was then quenched with 1 M acetic acid in methanol. After 5 min, pH 7 phosphate buffer was added, and the mixture was warmed to 25 °C. Extractive work-up with ethyl acetate and water, drying of the organic extracts with $MgSO_4$, and concentration *in vacuo* gave the crude product. Purification by medium-pressure liquid chromatography (silica gel, ethyl acetate/hexane gradient) gave 0.028 g (67%) of **8** as a colorless oil consisting of a 90:10 mixture of inseparable diastereomers. Major diastereomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.02-7.93 (m, 10 H, aromatic H's), 6.30 (dd, *J* = 15.6, 6.9 Hz, 1 H, C<u>H</u>=CHC=O), 5.07 (d, *J* = 15.6 Hz, 1 H, C=C<u>H</u>C=O), 4.80 (dt, *J* = 10.5, 4.2 Hz, 1 H, <u>H</u>CO, X_c), 3.11 (m, 1 H, C<u>H</u>H'SO_2), 2.98 (m, 1 H, CH<u>H</u>'SO_2), 2.83 (m, 1 H, C<u>H</u>CH_3), 1.27 (s, 3 H, C<u>H</u>$_3$CPh), 1.18 (s, 3 H, C<u>H</u>$_3$CPh), 1.17 (d, *J* = 6.9 Hz, 3 H, CHC<u>H</u>$_3$), 0.87 (d, *J* = 6.2 Hz, 3 H, CHC<u>H</u>$_3$, X_c), 0.64-2.05 (m, 8 H, X_c); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.11 (<u>C</u>=O), 151.81, 148.51, 139.73, 133.83, 128.90, 127.91, 127.83, 125.36, 124.73, 121.62 (aromatic and olefinic C's), 74.41 (O<u>C</u>H, X_c), 60.82 (<u>C</u>H$_2$SO$_2$), 50.34 (<u>C</u>HC(CH$_3$)$_2$Ph, X_c), 41.58 (<u>C</u>H$_2$, X_c), 39.53 (quat <u>C</u>, X_c), 34.53 (<u>C</u>H$_2$, X_c), 31.22 (<u>C</u>HCH$_3$), 28.46 (<u>C</u>HCH$_3$, X_c), 26.42 (<u>C</u>H$_3$, X_c), 24.24 (<u>C</u>H$_2$, X_c), 21.78 (<u>C</u>H$_3$, X_c), 19.27 (<u>C</u>H$_3$, X_c) [X_c = 8-phenylmenthyl chiral auxiliary]. The absolute configuration of product **8** was assigned by comparison with products from related kinetic resolutions of this type (see ref. 4c), and the enantiomeric purities of the diastereomers of **8** follow from the ≥98% stereoisomeric purity of the reagent **6** (see footnote 4). More definitive assignments for **8** and the derived **5a** will be made in later studies by direct correlation of derivatives from Schemes 2 and 3.
7. Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480-2482.
8. Thomas, E. J.; Whitehead, J. W. F. *J. Chem. Soc. Perkin Trans. 1* **1989**, 507-518.
9. Oikawa, M.; Ueno, T.; Oikawa, H.; Ichihara, A. *J. Org. Chem.* **1995**, *60*, 5048-5068.
10. Tanner, D.; Somfai, P. *Tetrahedron* **1987**, *43*, 4395-4406.
11. (a) Eggerer, H.; Grünewälder, C. *Justus Liebigs Ann. Chem.* **1964**, *677*, 200-208. (b) Wallach, O. *Justus Liebigs Ann. Chem.* **1878**, *193*, 1-61.
12. Buser, H. P.; Pugin, B.; Spindler, F.; Sutter, M. *Tetrahedron* **1991**, *47* (30), 5709-5716.
13. Finch, N.; Fitt, J. J.; Hsu, I. H. S. *J. Org. Chem.* **1975**, *40*, 206-215.
14. Green, D. L. C.; Kiddle, J. J.; Thompson, C. M. *Tetrahedron* **1995**, *51* (10), 2865-2874.
15. Roush, W. R.; Brown, B. B. *J. Org. Chem.* **1993**, *58*, 2151-2161.

(*Received in USA* 27 *May* 1997; *accepted* 8 *July* 1997)