Enantioselective Total Synthesis of (+)-Isolaurepinnacin

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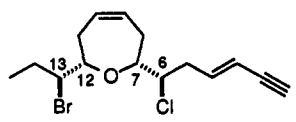
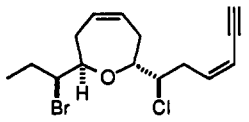
Red seaweeds of the genus *Laurencia* produce a wide variety of halogenated C_{15} acetogenins, which characteristically contain terminal enyne or bromoallene functionality.[2] The majority of these metabolites are oxygen heterocycles, with five- and eight-membered oxacycles occurring particularly widely.[2] Isolaurepinnacin (**1**)[3] and rogioloxepane A (**2**)[4] are examples of the rarer class of C_{15} *Laurencia* metabolites that contain seven-membered oxacyclic (oxepane) rings.[5] In this communication, we report

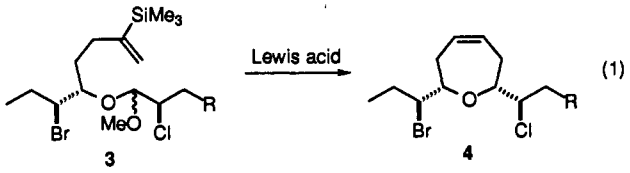


(+)-isolaurepinnacin (**1**)



(+)-rogioloxepane A (**2**)

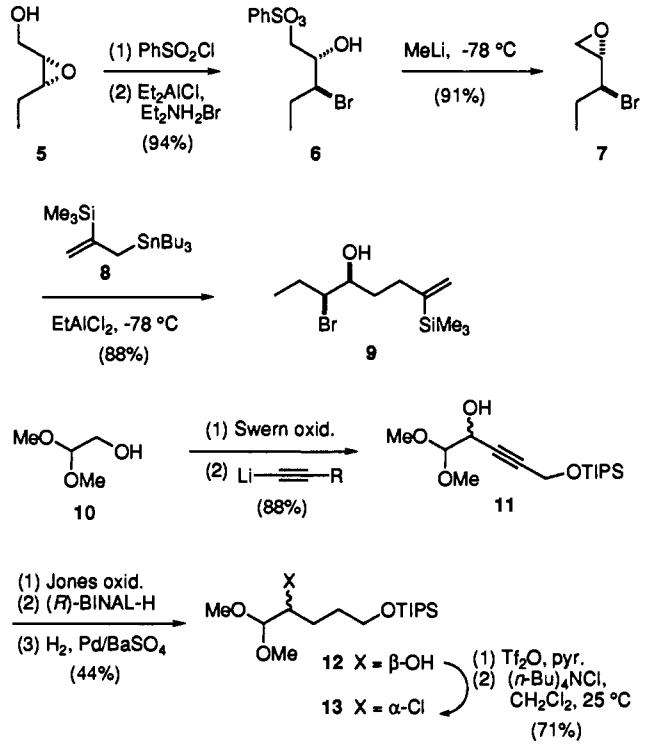
the first total synthesis of a *Laurencia* acetogenin of the oxepane group.[6] Our strategy was to form the *cis*-2,7-disubstituted Δ^4-oxepene ring of **1** by an acetal–alkene cyclization.[7] The defining reaction of the total synthesis of (+)-isolaurepinnacin recorded herein is the selective conversion of a β-chloro mixed acetal (**3**) to an oxepene (**4**) (eq 1), a conversion that effectively deals with all of the structural and stereochemical issues posed by this total synthesis target.[6d]



(1)

The syntheses of the (3*S*,4*S*)-vinylsilane alcohol **9** and the (*R*)-α-chloroacetal **13** precursors of the mixed acetal cyclization substrate **15** are summarized in Scheme I. Phenylsulfonylation of enantiopure epoxy alcohol **5**,[8–10] followed by regioselective

Scheme I



opening of the epoxy sulfonate derivative according to the procedure of Murai,[11] provided bromohydrin **6** in 94% yield.[12] Conversion of **6** to the volatile bromoepoxide **7** was best accomplished in ether by treatment at low temperature with MeLi. Although this epoxide does not react cleanly with 2-(trimethylsilyl)-2-propenyl cuprates or silanes, it does afford the desired vinylsilane alcohol **9** in high yield upon reaction at low temperature with the allyltin reagent **8** in the presence of $EtAlCl_2$.[13,14]

The (*R*)-α-chloroacetal **13** was prepared from commercially available 2,2-dimethoxyethanol (**10**) by Swern oxidation followed by *in situ* reaction of glyoxal dimethyl acetal with 3-(triisopropylsiloxy)propynyllithium to provide propargylic alcohol **11** in 88% yield.[15] Jones oxidation of this intermediate followed by enantioselective reduction[16] of the derived ketone provided (*S*)-**11** (80% ee).[17–19] Enantiopure (*S*)-**11** could be obtained from this material by chromatographic separation (and subsequent

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(2) Moore, R. E. In *Marine Natural Products*; Scheuer, P. J., Ed.; Academic: New York, 1978; Vol. 1, pp 43–121. Erickson, K. L. In *Marine Natural Products*; Scheuer, P. J., Ed.; Academic: New York, 1983; Vol. 5, pp 131–257.

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(5) For the isolation of other *Laurencia* oxepanes, see: (a) Kurosawa, A.; Irie, T. *Tetrahedron Lett.* **1973**, 4135. (b) Wratten, S. J.; Faulkner, D. J. *J. Org. Chem.* **1977**, *42*, 3343. (c) Suzuki, M.; Kurata, K.; Suzuki, T.; Kurosawa, E. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 2953. (d) Guella, G.; Pietra, F. *Helv. Chim. Acta* **1991**, *74*, 47. (e) Guella, G.; Mancini, I.; Chiasera, G.; Pietra, F. *Ibid.* **1992**, *75*, 303.

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(8) Sharpless epoxidation[9] of commercially available (*Z*)-2-pentenol gives **5** in 78% yield and 80% ee. Enantiopure **5** is obtained by recrystallization (and subsequent hydrolysis) of the 3,5-dinitrobenzoate derivative.[10]

(9) Rossiter, B. E.; Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1981**, *103*, 464. Evans, D. A.; Bender, S. L.; Morris, J. *Ibid.* **1988**, *110*, 2506.

(10) Chong, J. M. *Tetrahedron* **1989**, *45*, 623.

(11) Gao, L.; Saitoh, H.; Feng, F.; Murai, A. *Chem. Lett.* **1991**, 1787.

(12) All intermediates were fully characterized by ^1H and ^{13}C NMR, IR, and MS analysis. The elemental composition of analytical samples of new compounds was confirmed by combustion analysis or high-resolution mass spectrometry. Unless noted otherwise, yields refer to purified products.

(13) Allylstannane **8** was prepared in 54% overall yield from 1-(bromovinyl)-trimethylsilane by the following sequence: (a) Mg, THF; HCHO; (b) *n*-BuLi, THF, –60 °C; MsCl; (c) $LiSnBu_3$, THF, –78 °C. For a related sequence, see: Lee, E.; Yu, S.-G.; Hur, C.-U.; Yang, S.-M. *Tetrahedron Lett.* **1988**, *29*, 6969.

(14) Our investigations of the somewhat idiosyncratic reaction of α-halo epoxides with 2-silyl-2-propenyl organometallics will be published shortly: Overman, L. E.; Renhowe, P. A., manuscript in preparation.

(15) Bernard, D.; Doutheau, A.; Gore, J. *Synth. Commun.* **1987**, *17*, 1807.

(16) Noyori, R.; Tomino, I.; Tanimoto, Y.; Nishizawa, M. *J. Am. Chem. Soc.* **1984**, *106*, 6709.

(17) The α-acetal group apparently partially erodes enantioselection. Other catalytic and stoichiometric reductants (commonly used for the enantioselective reduction of ynones) that we screened gave lower enantioselectivities.

(18) The absolute configuration of (*S*)-**11** (which is opposite to that predicted by the typical model for stereoselective ketone reductions with BINAL-H[16] and undoubtedly results from the presence of the α-acetal functionality) was determined by chemical correlation with 1-methoxy-5-(triisopropylsiloxy)-2-pentanol. The comparison sample of (2*R*)-1-methoxy-5-(triisopropylsiloxy)-2-pentanol was prepared from 1-(triisopropylsiloxy)-4-pentene by the following sequence: (a) Sharpless asymmetic dihydroxylation (AD-mix-β),[19] *t*-BuOH, H_2O, 0 °C; (b) MeI, NaH, THF, 0 °C.

(19) Jacobsen, E. N.; Markó, I.; Mungall, W. S.; Schröder, G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 1968.

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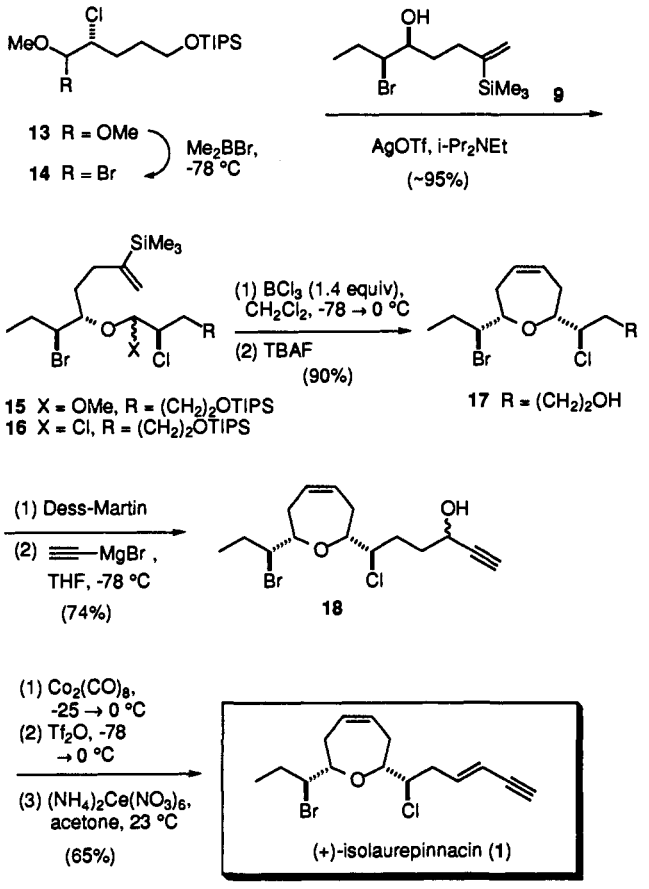
Scheme II



cleavage) of the diastereomeric carbamates derived from (*S*)-(−)-α-methylbenzyl isocyanate.[20] Catalytic hydrogenation of enantiomerically pure (*S*)-**11** then afforded enantiopure **12** in 44% overall yield from racemic propargylic alcohol **11**. Conversion of **12** to the triflate derivative followed by reaction of this intermediate with $(n\text{-Bu})_4NCl$ provided the (*R*)-α-chloroacetal **13** in 71% yield.[21]

The total synthesis of (+)-isolaurepinnacin was efficiently completed from the optically active fragments **9** and **13** as summarized in Scheme II. Treatment of acetal **13** at −78 °C with Me_2BBr, followed by removal of Me_2BOMe under reduced pressure, provided the corresponding α-bromo ether **14**.[22] This crude intermediate was directly combined with alcohol **9** in the presence of AgOTf to afford the mixed acetal **15** in high yield.[6d,23] Cyclization of this polyfunctional intermediate was best accomplished in CH_2Cl_2 by reaction with 1.4 equiv of BCl_3 at −78 → 0 °C.[6d] After desilylation of the crude cyclization product, *oxepene* **17** *was isolated in 90% overall yield from the β-chloroacetal.* This remarkably selective conversion proceeds by way of the α-chloro ether intermediate **16**,[24] which can be detected (and isolated) at short reaction times. The (*E*)-enyne side chain was then developed by initial oxidation of **17** with the Dess–Martin reagent,[25] followed by direct reaction of the resulting aldehyde with ethynylmagnesium bromide to afford **18**. Dehydration of this intermediate under a variety of standard conditions was not stereoselective. However, dehydration of the hexacarbonyldicobalt complex of **18** proceeded with high (>24:1) (*E*) stereoselection.[26] The optimal procedure was to initially convert **18** to the corresponding hexacarbonyldicobalt complex, which upon subsequent reaction in CH_2Cl_2 with Tf_2O afforded the hexacarbonyldicobalt complex of isolaurepinnacin. Decomplexation of this intermediate with ceric ammonium nitrate provided (+)-isolaurepinnacin (**1**), contaminated with less than 4% of its (*Z*) stereoisomer, in 65% overall yield from **18**. Synthetic **1** displays ^1H and ^{13}C NMR and IR spectra that are indistinguishable from those of the natural isolate and showed the following optical properties: $[\alpha]^{25}_D$ +0.6°, $[\alpha]^{25}_{546}$ +1.2°, $[\alpha]^{25}_{405}$ +3.2° (*c* = 1.4, $CHCl_3$).[27]

The first total synthesis of (+)-isolaurepinnacin has been achieved with high stereoselectivity in 12 steps and 15% overall yield from *cis*-2-penten-1-ol. This synthesis rigorously establishes the *S* configuration of **1** at C(13), which had previously been assigned on biosynthetic grounds, and corrects the rotation of **1** to be dextrorotatory.[28,29] Of particular note is the integrity of both bromine and chlorine functionalities during the Lewis acid-promoted cyclization of mixed acetal **15**; this conversion highlights the extraordinary selectivity that can be realized in acetal–alkene cyclizations. The formation of a single stereoisomer in this key conversion moreover demonstrates that chiral α-chlorooxocarbenium ions are sufficiently configurationally stable to not epimerize during a favorable acetal–alkene cyclization. This observation suggests that other oxacyclic marine natural products containing common 1-haloalkyl side chains can be accessed in asymmetric fashion by Prins-type cyclizations of β-haloacetals.

Acknowledgment. This investigation was supported by NSF Grant CHE-90-03812, and NMR and mass spectra were determined with spectrometers purchased with the assistance of NSF Shared Instrumentation Grants. We particularly thank Professor Akio Fukuzawa (Department of Engineering, Hokkaido Tokai University) for copies of spectra for natural isolaurepinnacin and for providing us with, and allowing us to report, unpublished information on the rotation of isolaurepinnacin and (3*Z*)-isolaurepinnacin isolated from *Laurencia pinnata* Yamada.

Supplementary Material Available: Listings of spectroscopic and analytical data for new compounds and copies of ^1H NMR spectra of synthetic isolaurepinnacin (5 pages). Ordering information is given on any current masthead page.

(20) Pirkle, W. H.; Hauske, J. R. *J. Org. Chem.* **1977**, *42*, 1839. Pirkle, W. H.; Hauske, J. R. *Ibid.* **1977**, *42*, 2781.

(21) We have no direct measure of the enantiomeric purity of this intermediate. However, the high yield of a single stereoisomer observed in the key cyclization confirms that the enantiopurity of **13** was high.[27]

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(23) Kronzer, F. J.; Schuerch, C. *Carbohydr. Res.* **1973**, *27*, 379.

(24) Goff, D. A.; Harris, R. N., III; Bottaro, J. C.; Bedford, C. D. *J. Org. Chem.* **1986**, *51*, 4711. Overman, L. E.; Thompson, A. S. *J. Am. Chem. Soc.* **1988**, *110*, 2248.

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(27) The C(6) epimer of **1**, which is available from cyclization of the mixed acetal formed from **9** and rac-**13**, is distinguishable from **1** by ^{13}C NMR and TLC comparisons.

(28) The small negative rotation, $[\alpha]^{25}_D$ −6.2° ($CHCl_3$), reported for **1** isolated from *Laurencia pinnata* Yamada is believed to be due to contamination from laurepinnacin, $[\alpha]^{25}_D$ −35.3° (*c* = 1.1, $CHCl_3$).[29] Co-occurring (3*Z*)-isolaurepinnacin showed a rotation of $[\alpha]^{25}_D$ +2.0° (*c* = 1.0, $CHCl_3$).[29] Desbromodeschlorooctahydroisolaurepinnacin prepared from synthetic (+)-**1** was dextrorotatory and, thus, in accord with the absolute configuration assignments of Kotsuki for this isolaurepinnacin degradation product.[6a]

(29) Fukuzawa, A., personal communication to L.E.O. of June 10, 1993.