Synthesis of (+)-Laurencin

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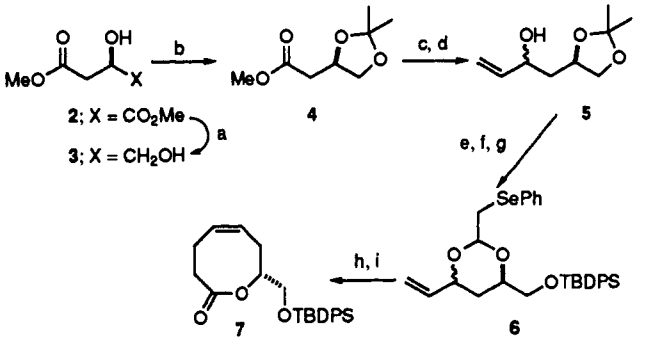
The wide occurrence of unsaturated medium ring ethers in a variety of *Laurencia* species and in the organisms which feed on this alga has become a feature of marine natural products chemistry.[1] The prototypical member of this family is undoubtedly (+)-laurencin (**1**), which was isolated from *Laurencia glandulifera* by Irie and Masamune[2] and was synthesized as the racemate in pioneering fashion by Masamune and co-workers some 17 years ago.[3] In this communication we report the enantioselective synthesis[4] of (+)-laurencin (**1**) in 26 steps from dimethyl (*R*)-malate (**2**) using a Claisen rearrangement approach to the key lactone **7**. Noteworthy steps are the reagent-controlled diastereoselective enolate oxidation, the carbon homologation sequence involving Tebbe methylenation of **7** and diastereoselective intramolecular hydrosilation, the stereocontrolled introduction of the pentenynyl side chain, and the remarkably high-yielding displacement of the secondary alcohol by bromide.

Of the various approaches to eight-membered medium ring ethers,[5] only the Overman[6] route to laurenyne has effectively employed the cyclization of an acyclic precursor to make a natural product; other popular approaches have relied on methods for elaboration of eight-membered lactone precursors.[7]

Selective reduction[8] of dimethyl (*R*)-malate (**2**) gave the diol **3**, which was protected as the acetonide **4** (Scheme I). DIBALH reduction of **4** followed by addition of vinylmagnesium bromide in the presence of cerium(III) chloride[9] to the distilled aldehyde gave the required allylic alcohol **5** as a 1:1 mixture of diastereoisomers (70%). Acetonide removal and *in situ* silylation of the primary hydroxyl group afforded a monoprotected triol which served as a precursor for the Claisen rearrangement.[10] Acetal formation with phenylselenoacetaldehyde diethyl acetal gave the dioxan **6** as a mixture of diastereoisomers. Oxidation with sodium metaperiodate gave the selenoxide, which was then heated to reflux in *m*-xylene (0.01 M) in the presence of DBU to afford the lactone **7** in 73% yield.

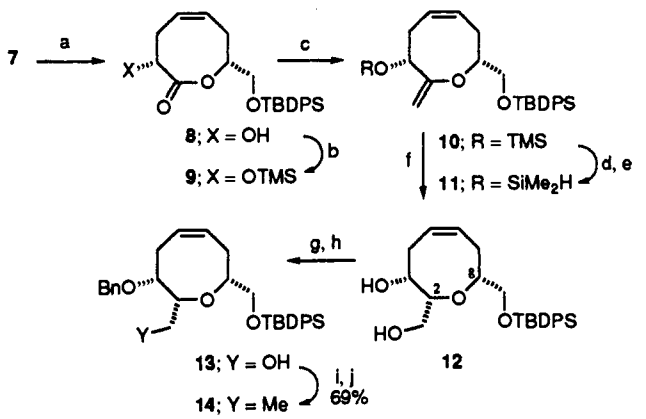
Formation of the enolate derived from **7** with potassium hexamethyldisilazide (KHMDS), followed by addition of (2*R*,8a*S*)-camphorsulfonyloxaziridine[11] (−78 °C) and quenching with camphorsulfonic acid (CSA, −40 °C to room temperature) gave the hydroxylactone **8** as a single diastereoisomer (Scheme II).[12] Our strategy for introduction of the ethyl side chain called for Tebbe methylenation[13] of the lactone carbonyl group and

Scheme I[a]



[a] (a) $BH_3{\cdot}Me_2S$, $NaBH_4$ (catalytic amount) (95%); (b) $CH_3C(OMe)=CH_2$, PPTS (90%); (c) DIBALH, THF, −78 °C; (d) $CH_2=CHMgBr$, $CeCl_3$, −78 °C (73% from **4**); (e) TsOH, MeOH, room temperature; (f) TBDPSCl, DMF, imidazole; (g) $PhSeCH_2C(OEt)_2$, Amberlite IR 120 resin (71% from **5**); (h) $NaIO_4$, $NaHCO_3$, room temperature, MeOH–H_2O; (i) DBU, *m*-xylene, reflux (73% from **6**).

Scheme II[a]



[a] (a) KHMDS, toluene, −78 °C, (+)-(2*R*,8a*S*)-camphorsulfonyloxaziridine, −78 °C, followed by CSA, −40 °C to room temperature (74%); (b) Me_3SiCl, Et_3N (91%); (c) Tebbe reagent, DMAP, −40 °C (71%); (d) TBAF, THF, 0 °C; (e) $(HMe_2Si)_2NH$, NH_4Cl (catalytic amount), 60 °C, (78% from **10**); (f) $Pt(DVS)_2$ (0.1 M in toluene, 2 mol %) THF, reflux, 16 h followed by EDTA·2Na·2H_2O–hexane and then KOH–H_2O_2 (65%); (g) $PhCH(OMe)_2$, PPTS; (h) DIBALH, CH_2Cl_2, −78 °C (58% from **12**); (i) TsCl, DMAP, CH_2Cl_2; (j) Me_2CuLi, C_6H_6/Et_2O (1:1), −78 °C (69% from **13**).

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(12) Oxidation with (*rac*)-2-(phenylsulfonyl)-3-phenyloxaziridine yielded a 1:1 mixture of diastereoisomers, indicating that the lactone enolate provided insufficient conformational bias.

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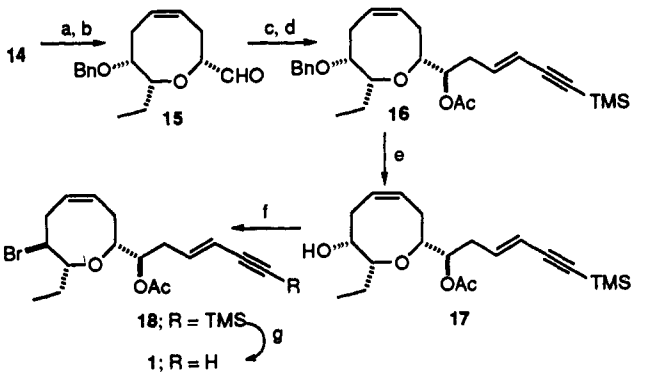
hydroxyl-directed intramolecular hydrosilation[14] of the enol ether. Protection of **8**, methylenation, and silyl group interchange afforded the enol ether **10** which was purified by flash chromatography on basic alumina. The key hydrosilation reaction was carried out by use of bis(1,3-divinyl-1,1,3,3-tetramethyldisiloxane)platinum(0) [$Pt(DVS)_2$][15] (2 mol %) in toluene to afford the required diol **12** and its 2β-hydroxymethyl epimer in a 3.5:1 ratio. The corresponding benzylidene acetal[16] was reductively cleaved with DIBALH[17] to give the differentially protected triol **13**, which was converted into the ethyl-substituted derivative **14** by coupling of the tosylate with lithium dimethyl cuprate.

Deprotection of the silyl ether **14** and Swern oxidation of the resulting primary alcohol yielded the aldehyde **15** in preparation for addition of the pentenynyl side chain (Scheme III). Addition of (*E*)-$LiCu(CH_2CH{=}CHC{\equiv}CSiMe_3)_2$[18] to the aldehyde **15** gave a 55:45 separable mixture of diastereoisomeric alcohols, the major isomer affording the acetate **16**. The minor diastereoisomer could be recycled to the required isomer by an oxidation–reduction sequence.[19] Debenzylation with boron trichloride–dimethyl sulfide complex[20] in dichloromethane at room temperature unmasked the secondary alcohol **17**,which was cleanly inverted to the bromo derivative **18** with DIPHOS–Br_2 in remarkably high yield.[21] Desilylation then yielded (+)-laurencin (**1**), mp 69–70 °C, $[\alpha]^{25}_D$ +69.0 (*c* 1.00, $CHCl_3$), which was identical in all spectroscopic data (IR, ^{1}H NMR, ^{13}C NMR, MS) to those of the natural and synthetic material.[22,23]

Scheme III[a]



[a] (a) TBAF, THF, 0 °C; (b) Swern oxidation (62% from **14**); (c) (*E*)-$LiCu(CH_2CH{=}CHC{\equiv}CTMS)_2$; (d) Ac_2O, pyridine, DMAP, CH_2Cl_2, 20 °C, (40% from **15**); (e) BCl_3·DMS, CH_2Cl_2, room temperature (76%); (f) $Ph_2PCH_2CH_2PPh_2$, Br_2 (70%); (g) TBAF–HF, pH 4, –15 to –10 °C, 15 min (93%).

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Supplementary Material Available: Details of the experimental procedure for the preparation **7**, **8**, **12**, and **16** and spectroscopic data for compounds **1**, **7**, **8**, **12**, **14**, **16**, and **17** (6 pages). Ordering information is given on any current masthead page.

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(16) The ^{1}H NMR spectrum of the benzylidene acetal derived from **12** showed a large apparent NOE between the methine protons H-2 (δ 3.14) and H-8 (δ 4.76) and a coupling constant (J = 4 Hz) between H-2 and H-3 (δ 4.76) consistent with a *cis* relationship between all substituents; the corresponding acetal of the the minor hydrosilation product showed no NOE between H-2 and H-8 and a characteristic *trans* diaxial coupling (J = 11 Hz) between H-2 and H-3. The ultimate assignment follows from the identity of synthetic **1** with the natural product.

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(18) This reagent was prepared from (*E*)-pent-2-en-4-ynol in four steps: (a) ^{n}BuLi, THF, –78 °C; (b) Me_3SiCl, –78 °C to room temperature (86%); (c) PBr_3, CH_2Cl_2, 0 °C (87%); (d) ^{t}BuLi, CuBr·Me_2S, –78 °C.

(19) The unwanted alcohol could be oxidized (Jones reagent) to the ketone, which was reduced[7d] with L-Selectride (Aldrich) to the required alcohol (>95:5 as judged by ^{1}H NMR).[4]

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(22) All new compounds exhibited satisfactory spectral and analytical and/or exact mass data. Yields refer to chromatographically and spectroscopically homogeneous materials.

(23) The standard abbreviations employed here can be found in *J. Org. Chem.* **1993**, *58*, 11A.