A Simple Enantioselective Synthesis of the Biologically Active Tetracyclic Marine Sesterterpene Scalarenedial

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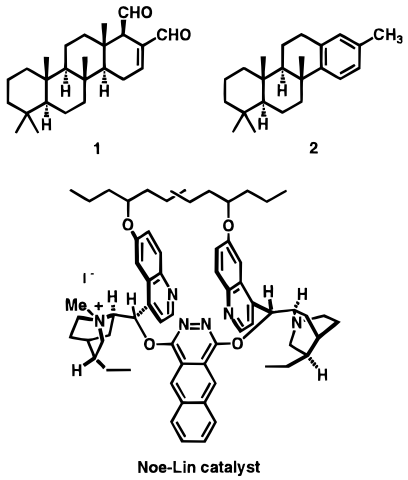
The sesterterpenoids of marine origin display impressive variety with respect to chemical structure and biological activity. The scalarane subfamily, which contains a characteristic 6/6/6/6-tetracarbocyclic fused ring system, includes members with multiple biological effects, for example, scalar-16-ene-19,20-dial (scalarenedial) (**1**)[1] displays not only potent fish anti-feedant properties but also antitumor and antiinflammatory effects.[1−7] The scalaranes are very ancient natural products as indicated by their widespread occurrence in petroleum and sea sediments in the form of the chiral hydrocarbon **2**.[8] We describe herein the first enantioselective total synthesis of **1** by a biomimetic route involving the simultaneous formation of all four carbocyclic rings. To the best of our knowledge this is the first example of a stereo- and enantiospecific tetracyclization reaction starting from a chiral oxirane (**8**).



A key to the synthesis is the availability of the mechanistically designed Noe-Lin catalyst for the catalytic enantio- and position-selective OsO_4-mediated dihydroxylation of geranylgeranyl acetate.[9] This catalytic oxygenation process proceeds with 50:1 position selectivity for the terminal double bond of geranylgeranyl acetate to form the (*R*)-diol with 95% enantiomeric purity under the influence of the Noe-Lin catalyst.[9] Monomesylate formation and K_2CO_3−MeOH cyclization[9] converted this diol to the (*S*)-oxirane **3** in 90% yield. The bromide **4** was produced from **3** by reaction with methanesulfonyl chloride−triethylamine−lithium bromide in tetrahydrofuran (THF) at −40 to 0 °C over 1 h and treated with the α-lithio derivative of **5**[10] (prepared from **5** and 1 equiv of lithium diisopropylamide, LDA) at −30 °C for 1 h to afford after mild acidic hydrolysis (biphasic pentane−H_2O−HOAc−NaOAc, 23 °C, 3 h) the acylsilane **6** in 89% yield.[10] Reaction of **6** with the α-sulfonyl lithio derivative of **7** (from **7** and 1 equiv of BuLi in THF−Et_2O−hexamethylphosphoramide (HMPA)) at −78 °C for 20 min and 0 °C for 10 min provided the silylated enol ether **8** (75%), the product of carbonyl addition of lithio-**7** to **6** followed by Brook rearrangement and β-elimination of benzenesulfinate ion.[10] Tetracyclization of **8** was carried out with $MeAlCl_2$ as Lewis acid catalyst in CH_2Cl_2 at −94 °C for 30 min to give, after sequential treatment of the crude product (**9**) with HF−H_2O−CH_3CN (to effect desilylation of the 3-hydroxyl group) and 10% KOH in MeOH (to effect $\alpha \rightarrow \beta$ equilibration of the side chain alpha to the D-ring carbonyl group) hydroxy ketone **10** in 30% overall yield (*ca.* 75% per ring formed).

The tetracyclic hydroxy ketone **10** was deoxygenated at C(3) by the Barton−McCombie process[11] to give **11** which was transformed into the vinyl triflate **12** by McMurry's method using potassium hexamethyldisilazane (KHMDS) as base.[12] Hydroxy desilylation[13] of **12** afforded the homoallylic primary alcohol which was carbonylated to the γ-lactone **13** using a Pd(0) 1,3-(bisdiphenylphosphino)propane (dppp) catalyst and 1 atm CO at 65 °C (94% overall from **12**). Scalarenedial **1** was then produced from **13** in two steps: (1) reduction with diisobutylaluminum hydride in CH_2Cl_2 to the corresponding diol (95% yield) and (2) Swern oxidation (90% yield). The synthetic scalarenedial **1** was identical with the natural product[1,7] by comparison of mp 203−204 °C (lit. 200−203 °C); rotation, $[\alpha]^{23}_D$ −20.7 (*c* 0.27, $CHCl_3$) (lit. $[\alpha]^{25}_D$ −19 (*c* 0.7, $CHCl_3$)); IR, ^1H NMR, ^{13}C NMR, and mass spectral data.

The unusual brevity of the synthesis of **1** which is described herein is a tribute to the power of several recently developed methods of synthesis including (1) the position- and enantioselective oxidation of geranylgeranyl acetate, (2) the rapid assembly and coupling reactions involving the acylsilane **6**,[10] (3) the tetracyclization **8** → **9**, and (4) the hydroxy desilylation and catalytic carbonylation which are perfectly suited to the introduction of the ene dial functionality in the D-ring of **1**.[14] Clearly, a substantial improvement in the efficiency of the

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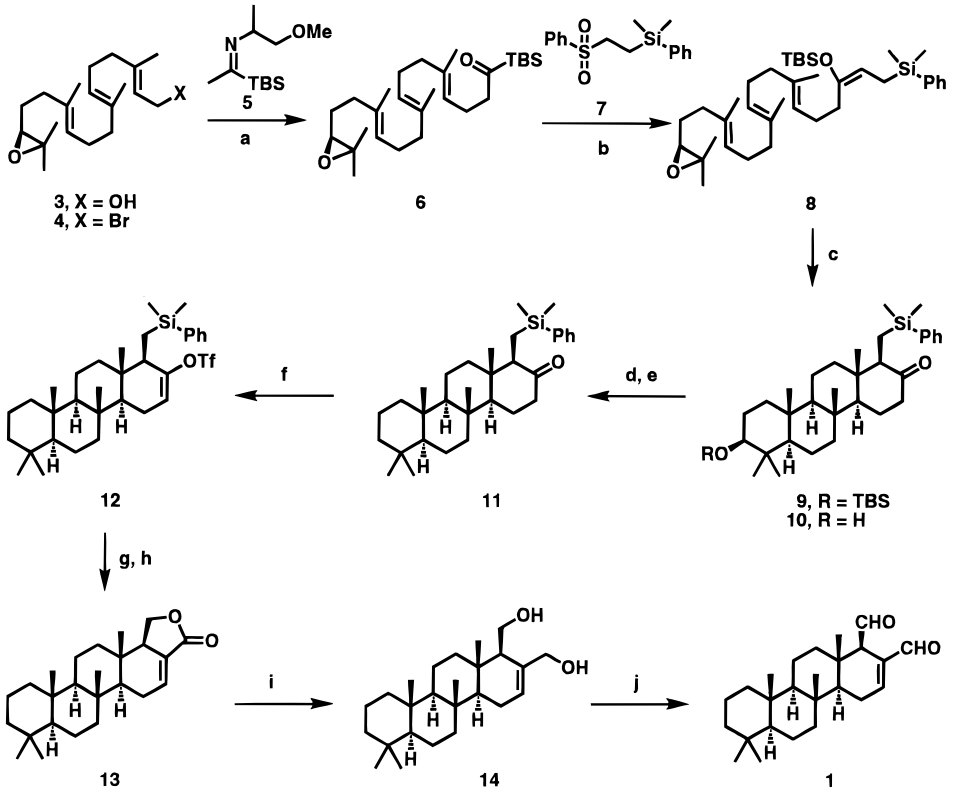
Scheme 1[a]



[a] (a) LDA, THF, −30 °C, 1 h; pentane−H_2O, AcONa−AcOH, 23 °C, 3 h, 89%. (b) *n*-BuLi, THF−Et_2O−HMPA (4.5:4.5:1), −78 °C, 20 min, 0 °C, 10 min, 75% at 80% conversion. (c) $MeAlCl_2$ (1.2 equiv), CH_2Cl_2, −94 °C, 30 min; CH_3CN, HF (aqueous); 10% KOH in MeOH, reflux, 3 h, 30%. (d) C_6F_5OCSCl (2 equiv), DMAP (3 equiv), CH_2Cl_2, 0−23 °C, 10 h, 95%. (e) Bu_3SnH (3 equiv), AlBN (0.1 equiv), benzene, reflux, 3 h, 94%. (f) $PhNTf_2$ (2.5 equiv), KHMDS (1.2 equiv), THF, −78 °C, 20 min, 90%. (g) BF_3·2AcOH (10 equiv), $CHCl_3$, 23 °C, 5 h; THF−MeOH (1:1), KF, $KHCO_3$, H_2O_2, 0−23 °C, 12 h, 94%. (h) $Pd(OAc)_2$ (0.1 equiv), dppp (0.1 equiv), CO (1 atm), *i*-Pr_2NEt (3 equiv), DMF, 65 °C, 5 h, 100%. (i) DIBAL-H (3 equiv), CH_2Cl_2, −78 to −20 °C, 1 h, 95%. (j) $(COCl)_2$ (10 equiv), DMSO (20 equiv), Et_3N (15 equiv), CH_2Cl_2, −50 °C, 1 h, 90%.

tetracyclization process (for example, to the level of 90% yield per ring formed) would constitute another noteworthy advance; studies in this direction are underway. Such an improvement, combined with the other methodology described herein, would allow synthetic access to several naturally occurring polycyclic polyprenoids which have hitherto been beyond the reach of chemical synthesis.

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Supporting Information Available: Experimental procedures and spectroscopic data for synthetic intermediates (13 pages). See any current masthead page for ordering and Internet access information.

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