pletely different regioselectivity, wherein a 1,4- rather than a 1,3-diene was obtained in the cycloisomerization and in the silver-promoted Heck cyclization. The route constitutes a reasonable strategy for the synthesis of cyclohexyl cores that can provide access to all the currently known saponaceolides. Its practicality is highlighted by its use in a successful synthesis of saponaceolide B.[21]

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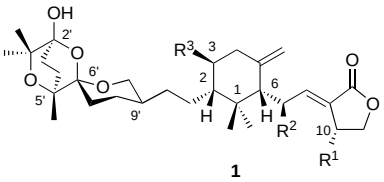
Total Synthesis of (+)-Saponaceolide B**

Barry M. Trost* and James R. Corte

The saponaceolides A – D (**1a** – **d**), discovered by Vidari and co-workers from the northern Italian mushroom *Tricholoma saponaceum*,[1] possess antitumor activity in 60 human cancer cell lines.[2] They possess several challenging structural



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a: R^1 = OH, R^2 = R^3 = H
b: R^1 = R^2 = R^3 = H
c: R^1 = R^2 = OH, R^3 = H
d: R^1 = R^3 = OH, R^2 = H

elements including the unique tricyclic trioxaspiroketal and a *cis* 2,6-disubstituted 1-methylene-3,3-dimethylcyclohexane ring. While a number of synthetic efforts have targeted portions of these structures,[2, 3] until recently only a synthesis of 2-*epi*-saponaceolide B has appeared, where the difficulties of controlling the ring configuration were highlighted.[4] We report here our efforts that have culminated in a synthesis of (+)-saponaceolide B (**1b**), a member that exhibits significant activity in four human cancer cell lines—leukemia K-562, nonsmall cell lung NCI-H23, melanoma LOX-IMVI, and SK-MEL-5.[2]

Scheme 1 illustrates the retrosynthetic analysis into the three subunits **2** – **4**. The central core unit **3** represents a significant challenge since the *cis* configuration at C2 and C6, which is thermodynamically less stable than the *trans* configuration, has proven difficult to access—a fact emphasized by the reported synthesis of only the 2-*epi* isomer.[4] The accompanying paper describes a synthesis of this unit.[13]

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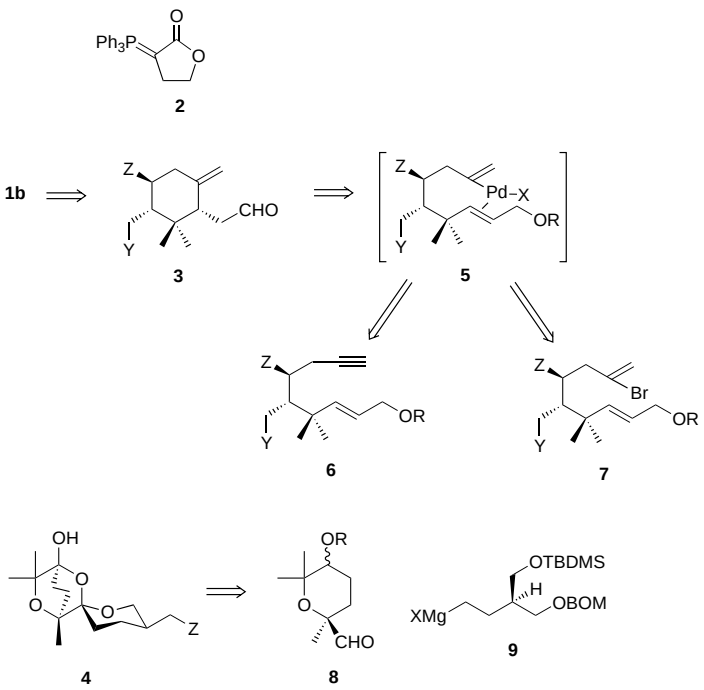
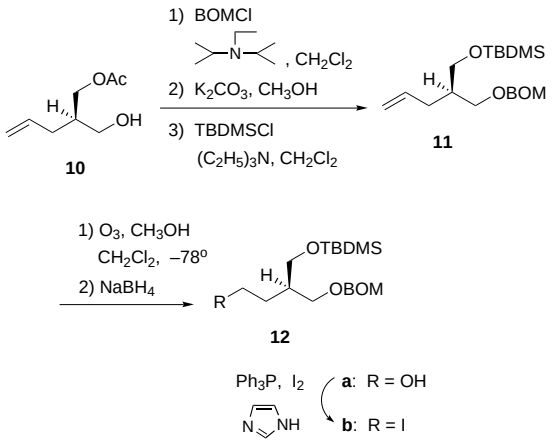


Scheme 1. Retrosynthesis of **1b**. TBDMS = *tert*-butyldimethylsilyl, BOM = benzyloxymethyl.

Here we record a synthesis of the spiroketal unit and the assemblage of the three fragments **2**–**4** to complete an asymmetric synthesis of (+)-saponaceolide B.

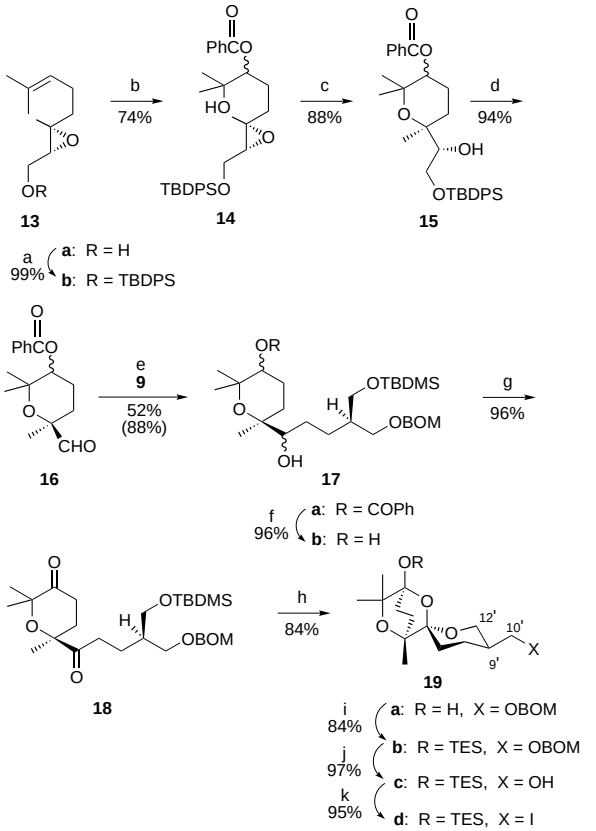
Schemes 2 and 3 outline the synthesis of the spiroketal portion starting from the known (*R*)-acetate **10**[5] and known geraniol epoxide **13a**.[6] The iodide precursor **12b** of the Grignard reagent **9** was derived from acetate **10** in straightforward fashion (Scheme 2). Protecting groups were incorporated in hydroxyacetate **10** by conversion into **11** (91 % overall



Scheme 2. Synthesis of the Grignard reagent precursor.

yield) to make the compound compatible for formation of an organomagnesium reagent. Oxidative cleavage with ozone and workup with borohydride furnished **12a** (83 % yield); subsequent iodination of **12a** to form **12b** (98 % yield) completes the synthesis of the iodide precursor of the Grignard reagent. The latter was generated by iodide–lithium exchange (2 equiv of *tert*-C_4H_9Li) followed by addition of magnesium bromide.

The aldehyde **16**, easily accessed from **14** via **15** as described by Vidari et al.[3a] followed by oxidative cleavage, proved to be the best intermediate for forming the entire carbon skeleton of the spiroketal unit (Scheme 3). While the lithium reagent derived from iodide **12b** added to **16**, better yields



Scheme 3. a) TBDPSCl, CH_2Cl_2, $(C_2H_5)_3N$, $-20\,^\circ C \rightarrow RT$; b) 5 mol % OsO_4, NMO, C_5H_5N, *tert*-C_4H_9OH, THF, RT; then $PhCO_2H$, DCC, DMAP, CH_2Cl_2, RT; c) CSA, CH_2Cl_2, $-15\,^\circ C \rightarrow RT$; d) TBAF, THF, RT, then $NaIO_4$, THF, H_2O, 0 °C; e) Et_2O, $-78\,^\circ C$; f) K_2CO_3, CH_3OH, RT; g) TPAP, NMO, 4-Å MS, CH_2Cl_2, RT; h) 1N aq. HCl, THF, RT; i) $TESOSO_2CF_3$, 2,6-lutidine, CH_2Cl_2, 0 °C; j) H_2, 10 % Pd/C, C_2H_5OAc; k) Ph_3P, I_2, imidazole, Et_2O, CH_3CN, 0 °C. NMO = *N*-methylmorpholin-*N*-oxide, DCC = dicyclohexylcarbodiimide, DMAP = 4-dimethylaminopyridine, CSA = camphersulfonic acid, TBAF = tetrabutylammonium fluoride, TES = triethylsilyl. Yields in parentheses are based upon recovered starting material.

were obtained with the organomagnesium reagent to give **17a**. Hydrolysis to diol **17b** followed by double oxidation with tetrapropylammonium perruthenate (TPAP)[7] produces the diketone **18**. The acyclic stereochemistry of diketone **18** directs the folding to place the alkoxymethyl group in an equatorial position. The correctness of this assertion is verified by the coupling constants between the proton on C9′ and the two protons on C12′ (saponaceolide numbering), which are consistent with an axial–axial ($J = 11$ Hz) and equatorial–axial coupling ($J = 5.0$ Hz). Functional-group manipulation by conversion of **19a** into the iodide **19d** sets the stage for the coupling.

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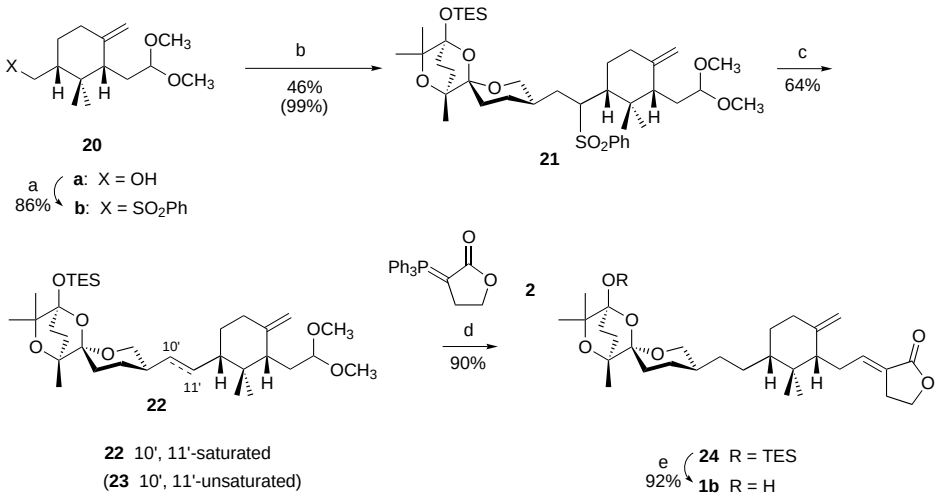

Scheme 4. a) $(C_4H_9)_3P$, PhSSPh, PhH, RT then TPAP, NMO, 4-Å MS, CH_3CN, 0 °C; b) n-C_4H_9Li, THF, HMPA, **19d**, $-55 \rightarrow -30$ °C; c) 5% Na(Hg), NaH_2PO_4, CH_3OH, -15 °C; d) CF_3CO_2H, THF, H_2O, RT, then **2** CH_2Cl_2, RT; e) TBAF, HOAc, THF, RT. HMPA = hexamethyl phosphoramide. Yields in parentheses are based upon recovered starting material.

Alkylation of a sulfone-stabilized anion was chosen for the coupling of fragments **3** and **4**. The sulfone **20b** was prepared from the corresponding alcohol **20a** in 86% yield by sulfide displacement followed by oxidation[8] (Scheme 4). The alkylation of sulfone **20b** with iodide **19d** proceeded nearly quantitatively at 50% conversion.

Reductive desulfonylation of **21** with sodium amalgam[9] gave **22** accompanied, surprisingly, by some elimination product **23**. That the alkene **23** did not form by base-catalyzed elimination is suggested by the absence of any dependence on the amount of added buffer nor on varying the reductant to samarium diiodide.[10, 11] The completion of the synthesis proceeded straightforwardly as outlined (Scheme 4). Olefination of the aldehyde liberated from the acetal **22** with the stabilized Wittig reagent **2**[12] gave a 13:1 ratio of the E:Z alkenes. The lower field shift ($\delta = 6.70$) of the new olefinic hydrogen of the major isomer compared to the minor one ($\delta = 6.19$) establishes the former as the E alkene. Desilylation then delivers synthetic saponaceolide B (**1b**, $[\alpha]_D^{22} = +14.4$, $c = 1.54$ in CH_2Cl_2), whose spectral data agrees well with those recorded for the natural product.[1] The success of this synthesis derived from its access to a stereodefined cyclohexyl unit, which in turn is prepared by the palladium-catalyzed cycloisomerization of enynes or the Heck protocol.[13] The convergent strategy should also provide access to other members of the saponaceolide family as well their analogues. The strategy outlined also provides opportunities to provide other natural products emanating from the cyclohexyl core **3**.

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Teaching Old Indicators New Tricks: A Colorimetric Chemosensing Ensemble for Tartrate/Malate in Beverages**

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The development of general methods for the colorimetric analysis of small and medium-sized analytes in solution is highly desirable since visual inspection yields immediate qualitative information, while absorption spectroscopy gives quantitative information. Many colorimetric assays exist, but most often they deal with the analysis of pH,[1] simple cations[2] and anions,[3] and radicals.[4] The majority of these sensors have the chromophore covalently attached to the recognition element. Upon binding of the analyte the electronic transitions of the chromophore are perturbed. In contrast, many colorimetric assays for large biological mole-

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