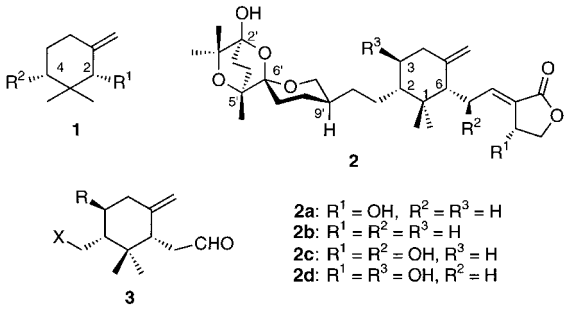
Towards the Total Synthesis of Saponaceolides: Synthesis of *cis*-2,4-Disubstituted 3,3-Dimethylmethylenecyclohexanes**

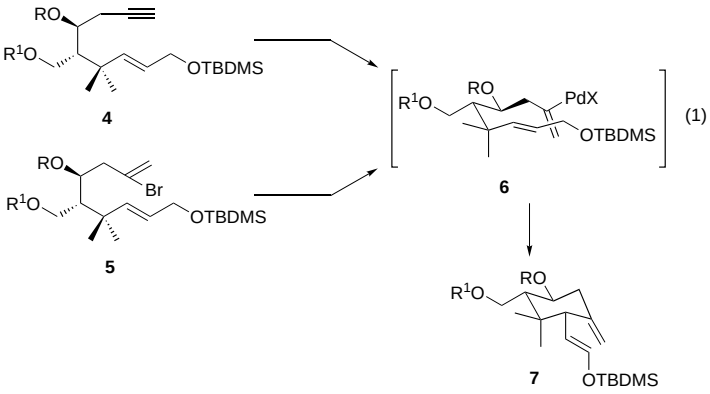
Barry M. Trost,* James R. Corte, and Mark S. Gudiksen

A variety of natural products are characterized by the cyclohexane structural unit **1**. For example, the cycloiridals are prized for their fragrance, and they show interesting activities such as potent piscicidal activity.[1] Carotenoids such as sarcinaxanthin also have this core unit.[2] The high cytotoxicity of saponaceolides A – D (**2a** – **d**) towards a large number of

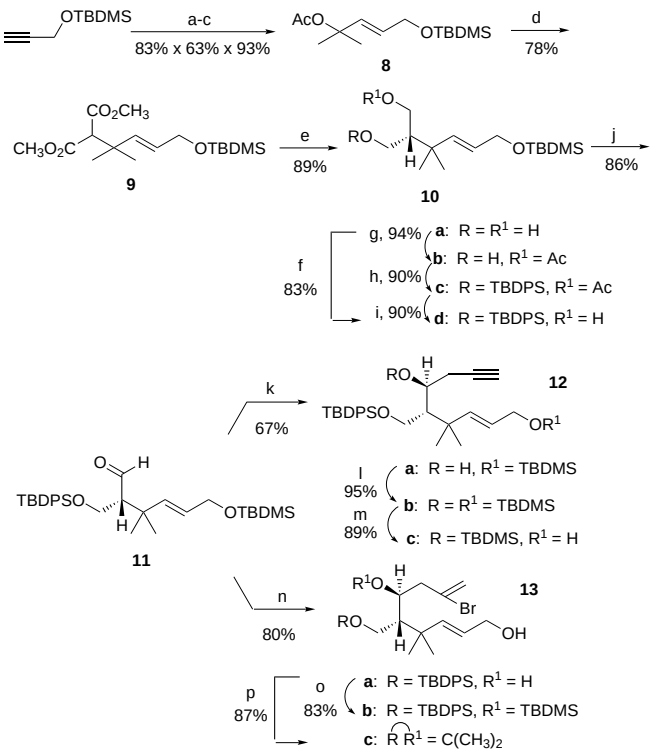


tumors focused our interest on the core unit of this family of compounds.[3, 4] While natural products have both *cis* and *trans* 2,4-substitution in **1**, all of the above-mentioned compounds show *cis* substitution. The fact that the *cis* isomer is the thermodynamically less stable isomer has hampered its access.[5] A recent report of the synthesis of 2-*epi*-saponaceolide B highlights this issue[6] and stimulated us to report our studies directed at this unit in the context of a total synthesis of the saponaceolides.

For a synthesis of the saponaceolides, the cyclohexyl system **3** serves as our target. Traditional strategies to structures like **1** based upon carbonyl chemistry that set the relative stereochemistry by base-catalyzed epimerization invariably led to the *trans* isomer.[5] Our interest in palladium-catalyzed cycloisomerizations of enynes[7, 8] led us to consider an alternative strategy to methylenecyclohexanes and raised the question of the geometrical constraints imposed by an intramolecular carbametalation. Simple modeling suggested that the intramolecular carbametalation via conformer **6** [Eq. (1); TBDMS = *tert*-butyldimethylsilyl] is 2.8 kcal mol^{-1} lower in energy than the alternative reaction leading to the *trans* product. In principal, this intermediate can be accessed by a cycloisomerization of enyne **4** or a Heck-type process with vinyl bromide **5**.



Scheme 1 outlines the synthesis of the cyclization precursors **4** (i.e., **12**) and **5** (i.e., **13**) in racemic form (the latter was



Scheme 1. a) *n*-C_4H_9Li, THF, −78 °C then CH_3COCH_3; b) Red-Al, Et_2O, 0 °C; c) Ac_2O, 5% DMAP, $(C_2H_5)_3N$, RT; d) $CH_2(CO_2CH_3)_2$, BSA, 5% $[Mo(CO)_6]$, $PhCH_3$, reflux; e) LAH, THF, 0 °C; f) NaH, THF, 55 °C then TBDPSCl, RT; g) PCL (Amano), CH_2=CHOAc, THF, RT; h) TBDPSCl, imidazole, DMF, 0 °C; i) $Ba(OH)_2$, CH_3OH, RT; j) 5% TPAP, NMO, 3-Å MS, CH_2Cl_2, 0 °C; k) CH_2=C=CHMgBr, Et_2O, −78 °C; l) TBDMSO-SO_2CF_3, 2,6-lutidine, CH_2Cl_2, 0 °C; m) C_2H_5OH, PPTS, 50 °C; n) CH_2=C(Br)CH_2Br, Sn, HBr, Et_2O, H_2O, RT; o) same as (l) then C_2H_5OH, PPTS, 55 °C; p) TBAF, THF, RT, then CH_3COCH_3, amberlyst 15-H^+, RT. DMAP = 4-dimethylaminopyridine, BSA = *N*,*O*-bis(trimethylsilyl)acetamide, TBDPS = *tert*-butyldiphenylsilyl, TPAP = tetrapropylammonium perruthenate, NMO = *N*-methylmorpholin-*N*-oxide, PPTS = pyridinium *p*-toluenesulfonate, TBAF = tetrabutylammonium fluoride.

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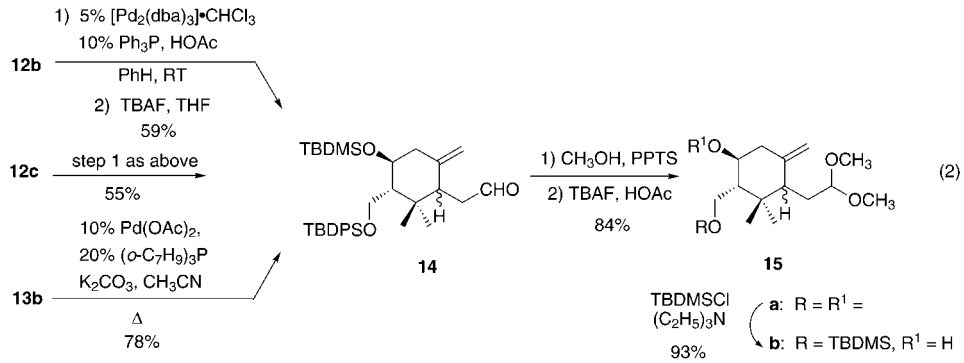
obtained in enantiomerically enriched form as well). Introduction of the malonate moiety regioselectively by allylic alkylation with acetate **8** takes advantage of the bias of molybdenum catalysts to direct nucleophilic attack towards the more highly substituted allyl terminus; regioisomer **9** is the exclusive product.[9]

The racemic silyl ether **10d** is available directly from the diol **10a** by the method of McDougal et al.[10] Enantiomerically enriched monoacetate **10b** is obtained by enzymatic transesterification with 86% ee (45% yield, 91% yield based on recovered starting material) with *Pseudomonas fluorescens* lipase (PFL).[11] With *Pseudomonas cepacia* lipase (PCL)[12] higher conversions (68% yield, 94% yield based on recovered starting material) are obtained, but with a slightly lower *ee* value (81% *ee*). The absolute configuration was established by the known stereochemical preferences of the enzymes employed and verified by correlation with a known compound.[13] Interestingly, organometallic additions to aldehyde **11** proceeded completely diastereoselectively with allenylmagnesium bromide[14] to give **12** and with tin and 2,3-dibromopropene[15] under Barbier conditions to give **13**. The relative configuration in both cases was established by converting the 1,3-diol units into cyclic acetonides (**13c** in the latter case), and NMR spectroscopy verifies the *trans* relationship of the two methine hydrogen atoms (for **13c**, J = 9.2 Hz). This stereochemistry corresponds to a Felkin–Anh mode of addition.[16]

Previous work suggests that the cycloisomerization of substrates like **12** should produce 1,3- rather than 1,4-dienes.[7, 17] In contrast to this expectation, palladium-catalyzed cycloisomerization of **12b** proceeded to form exclusively the 1,4-diene product, an enol silyl ether, which is directly hydrolyzed to the aldehyde **14** [Eq. (2); dba = dibenzylideneacetone]. Alternatively, cycloisomerization of **12c** provides the aldehyde **14** directly as the sole product. In both cases, the product is isolated as a 2:1 mixture in which the major isomer indeed has the desired *cis* configuration (see below).

To compare the two processes, the corresponding Heck reactions of vinyl bromides **13b** and **13c** were examined. Cyclization of **13b** to **14** proceeded smoothly to generate a poorer 1:1 ratio of the *cis*:*trans* products **14** [Eq. (2)].[18] On the other hand, the rigid acetonide **13c** leads to the cyclization product **16** in a *cis*:*trans* ratio as high as 2.4:1. Efforts to further increase this ratio failed. Preparatively, the highest yield (53%) of the *cis* isomer stemmed from the conditions[19] illustrated in Equation (3) in which a *cis*:*trans* ratio of 2:1 was observed (dppb = 1,4-bis(diphenylphosphanyl)butane, DMA = *N*,*N*-dimethylacetamide). Methanolysis of **16** resulted in conversion into **15a**.



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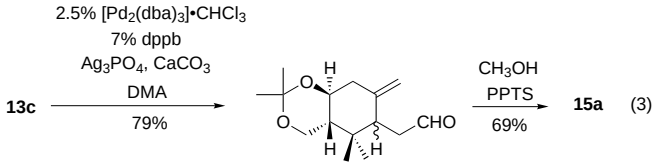
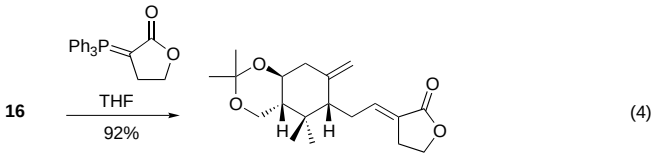


(3)

16

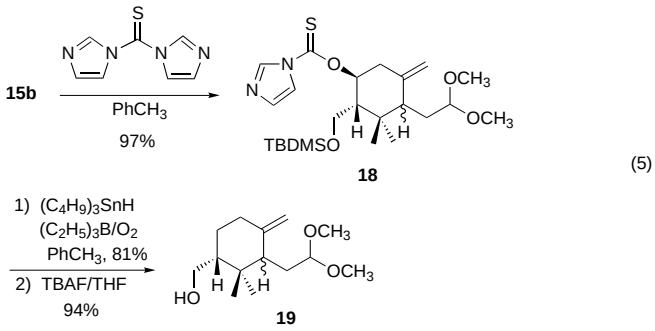
To establish the relative configuration, the aldehyde **16** was converted into **17** [Eq. (4)], which corresponds to the right-hand portion of deoxysaponaceolide D. X-ray crystallography established the full stereochemistry as depicted. The diol **15a** may serve as a general intermediate for the synthesis of



(4)

17

saponaceolides. While saponaceolide D requires retention of both hydroxyl groups, the syntheses of saponaceolides A–C require the removal of the free hydroxyl group from the monosilyl ether **15b**. For this purpose, we turned to free radical chemistry [Eq. (5)]. The reaction proceeded unevent-



(5)

fully via thionocarbamate **18** to give the saponaceolide intermediate **19**.[20] The pure *cis* isomer can be isolated at the stage of the diol **15a**, its monosilyl ether **15b**, or the monoalcohol **19**. Practically, the separation was best done with alcohol **19**.

The palladium-catalyzed cycloisomerization and Heck reactions described here provide the best route to date for the formation of the requisite *cis*-3,3-dimethyl-2,4-disubstituted methylenecyclohexyl unit **1** common to many natural products. The unusual nature of this core unit is further illustrated by the com-

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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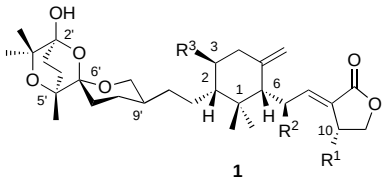
Total Synthesis of (+)-Saponaceolide B**

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



1

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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