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Total Synthesis of (±)-Bisabosqual A

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Abstract

The synthesis of the novel squalene synthase inhibitor, bisabosqual A, was completed in 14 steps (longest linear sequence) from commercially available starting materials. The doubly convergent route employs a tandem 5-exo, 6-exo radical cyclization as the key step. This reaction assembles the fully functionalized tetracyclic core and introduces three stereogenic centers. Other effective transformations are the regioselective deoxygenation of an advanced enone intermediate and the chemo- and diastereoselective addition of trimethylaluminum to a ketone in the presence of esters.

The bisabosquals A-D (**1-4,** Figure 1)[1] are *Stachybotrys* metabolites that were isolated in a screen for inhibition of microsomal squalene synthase. They were shown to be active against fungal squalene synthases from *Saccharomyces cerevisiae* and *Candida albicans*. In addition, they were found to be inhibitors of squalene synthases from rat liver and HepG2 cells with activities in the low micromolar range. Inhibtors of mammalian squalene synthases are of interest as antihypercholesteremic agents.[2]

The bisabosquals have unusual and complex architectures. Among natural products, they are unique in that they contain the hexahydrobenzofurobenzopyran ring system.[3] In addition, the phthalaldehyde moiety, contained in bisabosquals A, C, and D, is a rare structural motif, found in only a few natural products.[4] Most of these, including the well known complement inhibitor K-76, were also isolated from *Stachybotrys*.[4a]

As synthetic targets the bisabosquals are challenging; in each case, the *cis*, *cis*-fused tetracyclic ring system contains five contiguous stereogenic centers, two of which are quaternary. To date, only Snider and coworkers[5] have published an approach to this structural and stereochemical array. Snider's noteworthy biomimetic strategy, based on an inverse electron demand Diels Alder reaction followed by an oxidative cyclization, produced the bisabosqual core.

Our own approach stems from our recognition of the utility of tandem radical cyclizations for the efficient construction of *cis*, *cis* tetracycles with topologies similar to that required for the bisabosquals.[6] Herein we describe the successful development of this design concept in the context of the first total synthesis of (±)-bisabosqual A (**1**).

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Supporting Information Experimental procedures, spectroscopic, characterization and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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Retrosynthetic analysis of a diester synthon **5**, a likely precursor of bisabosqual A, led us to propose a regio- and stereoselective cascade based on an aryl radical **Rad-1** (Scheme 1). A 5-exo closure of **Rad-1** would afford the tricyclic **Rad-2** with the required *cis* junction as a result of geometric constraints. **Rad-2** can participate in a 6-exo addition to the enol ether double bond from either of the two accessible reactive conformations (**A** and **B**). The radical center is available for this interaction only on the concave surface of the ring system. However, *a priori*, it was difficult to predict whether attack on one face of the enol ether double bond would be favored. Thus, closure to the tetracyclic **Rad-3** and subsequent reductive trapping was expected to afford the tetracycle **6** with the *cis, cis* ring system but it would not necessarily control stereochemistry at C-7.

Nonetheless, the attraction of this approach was significant. The assembly of structure **7** would be available through a doubly convergent scheme based on readily available compounds **8**, **9**, and a precursor of the enol ether side chain.

We considered simple enol ethers (see **7a**) as well as vinylogous esters (e.g. **7b**) for the C-6′ oxygen substituent in the cyclization substrate (Scheme 1). Although the use of a vinylogous ester would require the eventual removal of the oxygen functionality at C-9, we settled on this option because of the expected convenience of substituent introduction, stability of intermediates, and anticipated efficiency of the **Rad-2** to **Rad-3** step. Therefore, we selected enynone **10** as the precursor to the side chain appendage.

The requisite starting materials were readily obtained. Iodination of the well known diester **11**[7] (two steps from methyl 3-trimethylsiloxy-2-butenoate) by application of the iodine/periodic acid protocol of Hathaway[8] provided the pentasubstituted rescorcinol **8** in 84% yield (Scheme 2). Monoprotected diol **9** was the major diastereomer obtained when ketone **12** (two steps from cyclohexenone)[9] was subjected to the reducing system of Utimoto.[10] Enynone **10** was prepared in two steps (from 3-methyl-2-butenoic acid) by a modification of the method of Jacobi.[11] The details of these preparations are contained in the Supporting Information.

The radical precursor **7b** was easily assembled via a two step approach (Scheme 2). A DABCO-catalyzed, regioselective 1,4-addition[12] of resorcinol **8** to acetylenic ketone **10** installed the vinylogous ester sidechain, giving exclusively the *E*-isomer **13** in 70% yield; see Figure 2 for the X-ray structure. Mitsunobu reaction[13] of phenol **13** with alcohol **9** afforded the radical cyclization substrate **7b** in 96% yield. The short synthesis of this key intermediate could be carried out on multi-gram scales.

We required an efficient and convenient procedure for the tandem radical cyclization of substrate **7b** to tetracycle **6b** (Scheme 2). After some experimentation, we identified treatment with *s*-Bu_3B and $(TMS)_3SiH$ in the presence of air[14] as an excellent protocol for providing the *cis, cis*-fused tetracyclic core **6b** on a gram scale. This cyclization proceeds in 72% yield with complete selectivity at C-5 and C-6 while providing a 3:2 mixture of epimers at the quaternary center (C-7). Stereochemistry was assigned to each isomer by NOE analysis; refer to Supporting Information for details. Notably, the minor epimer could easily be converted into a 2:1 mixture of **6b** and C-7-*epi*-**6b** by treatment with the guanidine

base 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD). Incorporation of this procedure into the synthetic scheme contributes to its overall efficiency.

With the tetracyclic ketone **6b** in hand, we sought a method to remove the oxygen functionality at C-9 (Scheme 3). We were drawn to the mild conditions described by Trost for the regioselective deoxygenation of an allylic carbonate with a similar substitution pattern.[15] Toward this end, Luche reduction[16] of ketone **6b** followed by acetylation provided **14** which was treated directly with $[PdCl(allyl)]_2$, phosphite **15**, and L-selectride. This procedure, optimized for our system by the rapid addition of L-selectride, provided the desired **16** in excellent yield (86% for three steps) with only a trace of the product of olefin migration.

Completion of the synthesis required modification of the functionality at carbons 3, 7′, and 8′. Liberation of the secondary alcohol at C-3 with tetrabutylammonium fluoride (TBAF) followed by Dess-Martin periodinane oxidation[17] cleanly delivered ketone **17** in 88% yield for two steps (Scheme 3). Exploratory attempts to add methylmagnesium bromide to the keto group suggested that this reagent was not selective for a single product. However, trimethylaluminum smoothly provided the anticipated tertiary alcohol **5** as a single diastereomer.[18] Unambiguous assignment of the five stereogenic centers was confirmed by X-ray crystallography of this diester (**5**, Figure 2).

All that remained was elaboration of the phthalaldehyde functionality (Scheme 3). Reduction of diester **5** with lithium aluminum hydride provided a diol which was unstable to purification; consequently it was used directly in the next step. For the preparation of the dialdehyde, Dess-Martin oxidation[19] was found to be superior to Swern or barium manganate conditions,[20] cleanly providing bisabosqual A (**1**) in 81% yield for the two steps. The ^{1}H-NMR and ^{13}C-NMR spectroscopic data of this product were indistinguishable from those reported for naturally occurring (+)-bisabosqual A. Moreover, the structure of bisabosqual A (**1**) was further confirmed by X-ray crystallographic analysis (Figure 2).

This total synthesis of (±)-bisabosqual A (**1**) is the first synthesis of a bisabosqual. The key step, a 5-exo, 6-exo radical cyclization, provides two rings and sets three of the five stereogenic centers (two of them with complete specificity) in the product. This approach showcases the power of radical cyclizations to access complex polycyclic ring systems. It also highlights the functional group selectivity of the trimethylaluminum reagent and the high regioselectivity of the Trost-Hutchins reducing system. The synthesis requires 14 steps (longest linear sequence) from commercially available materials. The approach can be easily adapted to an asymmetric synthesis and it offers access to a variety of structural analogs. The pursuit of these goals is currently underway.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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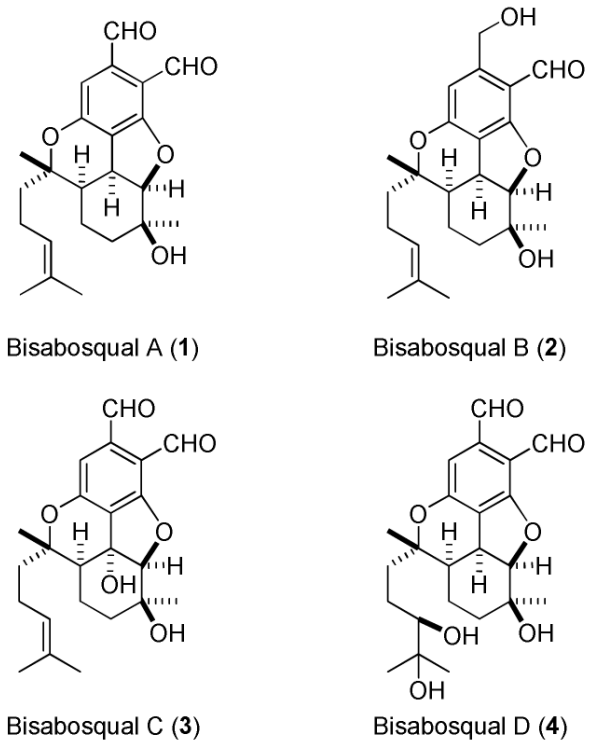


Figure 1.
The Bisabosquals A-D (**1**-**4**)

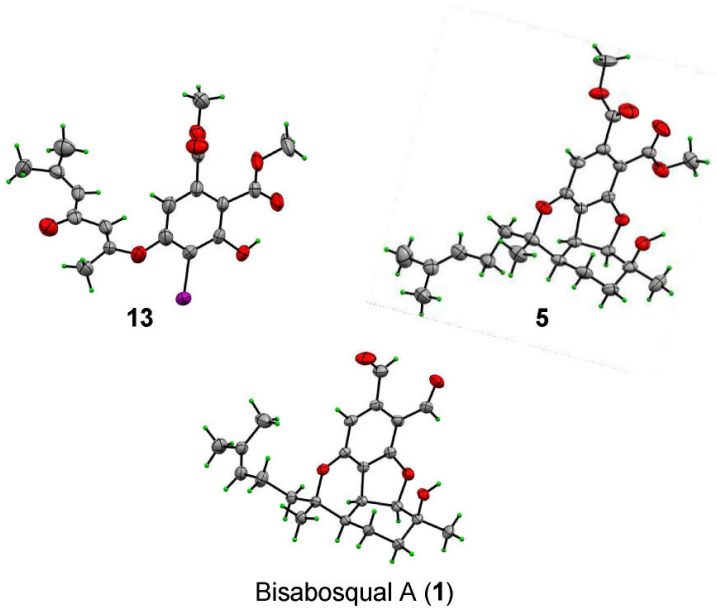
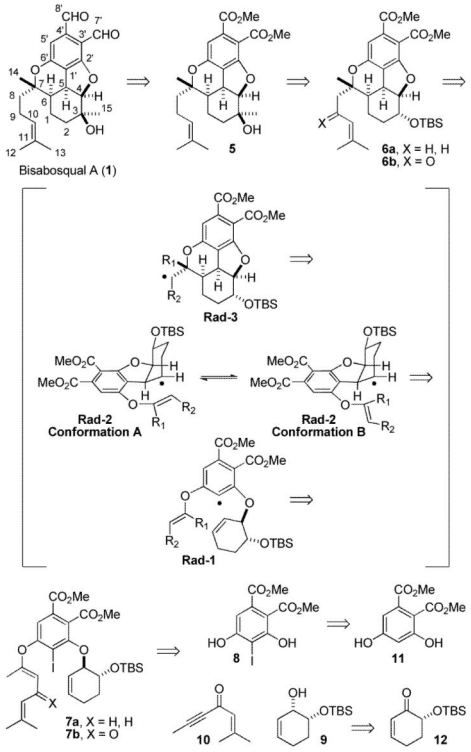


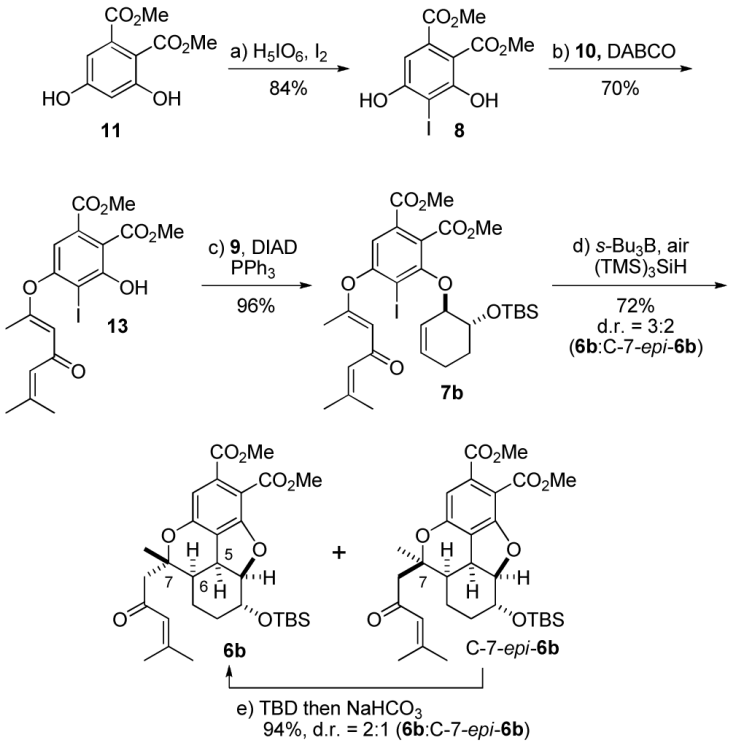
Figure 2.

X-Ray structures of **13**, **5**, and bisabosqual A (**1**). Non-hydrogen atoms are displayed at a 50% probability level.



Scheme 1.

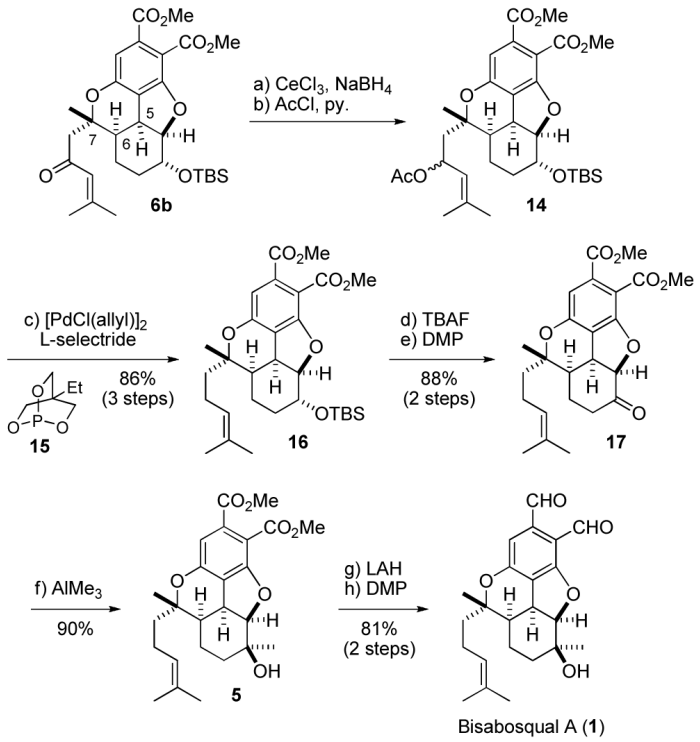
Retrosynthetic Analysis of Bisabosqual A and Conformational Analysis of the Radical Intermediates in the Key Cyclization



Scheme 2.

Convergent Assembly of Bisabosqual Tetracycle 6b[a]

[a]Reagents and conditions: (a) H_5IO_6, I_2, EtOH, H_2O, r.t., 6 h, 84% (b) **10**, DABCO (0.2 equiv), THF, r.t., 80 h, 70%; (c) **9**, DIAD, PPh_3, THF, r.t., 6 h, 96%; (d) *s*-Bu_3B (1M in THF), $(TMS)_3SiH$, air, CH_2Cl_2, r.t., 45 min, 72%, d.r. = 3:2 (**6b**:C_7-*epi*-**6b**); (e) TBD, THF, r.t., 15 min, then $NaHCO_3$, r.t., 2 h, 94%, d.r. = 2:1 (**6b**:C-7-*epi*-**6b**).



Scheme 3.

Elaboration of Bisabosqual A[a]

[a]Reagents and conditions: (a) $CeCl_3 \cdot 7H_2O$, $NaBH_4$, MeOH, −78 °C → 0 °C, 1 h; (b) AcCl, pyridine, CH_2Cl_2, 0 °C, 30 min; (c) **15**, $[PdCl(allyl)]_2$, L-selectride (1M in THF), 0 °C, 15 min, 86% (3 steps); (d) TBAF (1M in THF), THF, r.t., 1 h; (e) Dess-Martin periodinane, CH_2Cl_2, r.t., 1 h; (f) $AlMe_3$ (2M in heptane), toluene, 0 °C → r.t., 30 min, 90%; (g) LAH (1M in THF), THF, 0 °C, 45 min; (h) Dess-Martin periodinane, CH_2Cl_2, 0 °C → r.t., 1 h, 81% (2 steps).