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New Efficient Route to an Advanced Precursor of the AB Spiroketal of Spongistatins

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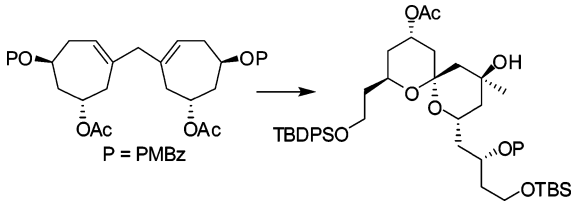
ABSTRACT



A sequence of highly diastereoselective functionalizations allowed transformation of a *meso*-methylenebis(cyclohept-3-ene-1,6-diyl diester) into an advanced precursor of the AB spiroketal of spongistatins. This route illustrates the potential of this bis-cycloheptene derivative for the synthesis of a key fragment of complex bioactive natural compounds.

Spiroketals and, in particular, 6,6-congeners are key structural features of a variety of natural products of biological interest. In particular, spongistatins (altohyrtins), which were isolated in 1993 by three research groups[1] from marine sponges of the genus *Spongia*, present two highly functionalized 6,6-spiroketal subunits in their skeleton (Figure 1). The highly potent antitumor activity of these compounds[2] combined with their impressive architectures and their extremely low natural abundance prompted organic chemists to develop strategies to face the synthetic challenge of their preparation. Several total syntheses[3] have been reported,[4] and many routes to key subunits have also been described.

In particular, considerable efforts have been devoted to the efficient preparation of the axial/axial AB and axial/equatorial CD spiroketals and on the EF tetrahydropyran fragment.[5] Recently, a noniterative methodology has been developed in our group for the asymmetric synthesis of C_{15} polyketides from readily available 2,2′-methylenedifuran.[6] This method was applied to the synthesis of the polyol

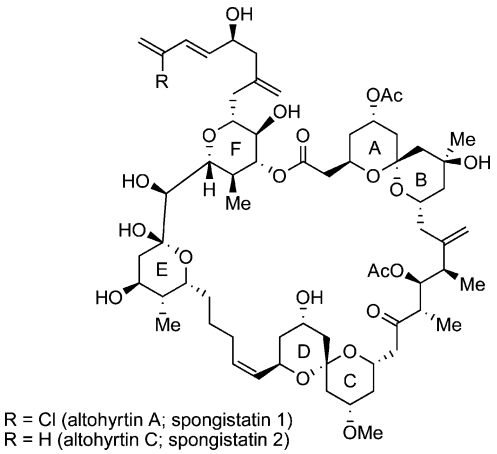


Figure 1. Altohyrtins and spongistatins.

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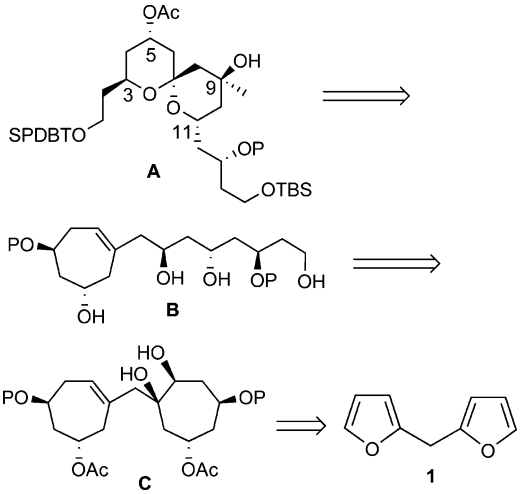
Scheme 1. Retrosynthetic Plan

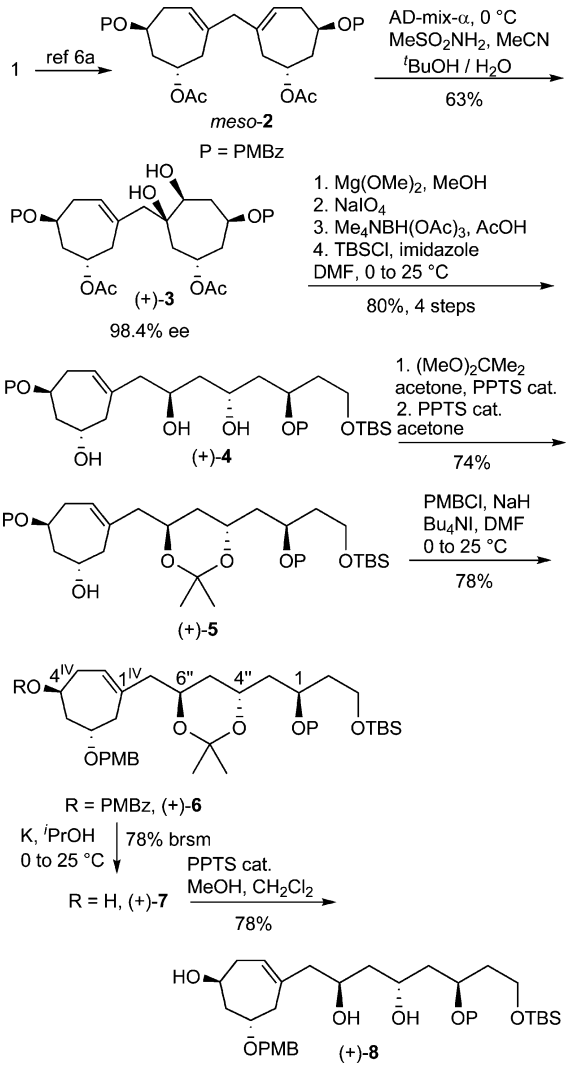


subunit of the polyene macrolide antibiotic RK-397[7] and to the generation of C_{15} polyketide spiroketals.[8]

We report here a new application of this versatile methodology to the synthesis of an advanced precursor **A** of the AB spiroketal of spongistatins which was planned from functionalized cycloheptene **B** through oxidative cleavage of the olefin, selective reduction of the resulting aldehyde, and spiroketalization under acidic conditions (Scheme 1). Intermediate **B** should arise from enantiomerically pure diol **C** that will be produced from 2,2′-methylenedifuran (**1**) through a double [4 + 3]-cycloaddition followed by desymmetrization of the *meso* bisadduct isomer.

Difuryl derivative **1** was converted into diolefin *meso*-**2** as previously reported,[6a] and desymmetrization of this intermediate was achieved by Sharpless asymmetric dihydroxylation,[9] in the presence of an enriched AD-mix-α, to afford diol **3** with 98.4% ee (Scheme 2). The diastereoisomeric diol was isolated in 16% yield, but its enantiomeric excess was only 4%.

Scheme 2



meric diol was isolated in 16% yield, but its enantiomeric excess was only 4%.

A four-step sequence, involving methanolysis of the acetyl groups, oxidative cleavage of the diol moiety, followed by diastereoselective reduction of the oxo-aldehyde intermediate under Evans conditions[10] and selective silylation of the primary alcohol, afforded triol (+)-**4** with 80% overall yield.

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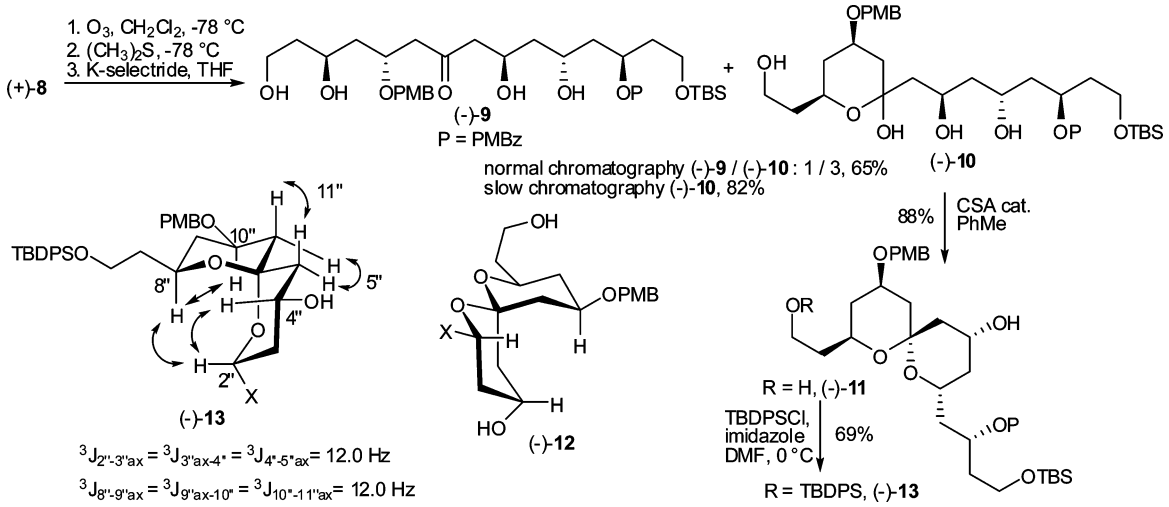
Scheme 3. Spiroketalization



Transformation of the 1,3-*anti*-diol as the corresponding acetonide and subsequent etherification of the remaining secondary alcohol provided the orthogonally protected hexol (+)-**6** in 58% yield (two steps). At this stage, the selective saponification of the C(4^{IV})-*p*-methoxy benzoate (PMBz) was investigated. Several alcoholates were assayed (MeOK, 2-BuOK, 2,2-dimethyl-3-pentanolate, 3-pentanolate) but led to low discrimination between the two *p*-methoxy benzoate moieties. In situ generated potassium isopropoxide was the most efficient base and furnished alcohol (+)-**7** in 78% yield based on recovered starting material (brsm) (47% yield). Triol (+)-**8** was then obtained by acidic methanolysis of the acetonide moiety.

In a first series of attempts, ozonolysis of the olefin moiety of (+)-**8** followed by reductive treatment, first with dimethyl sulfide then with K-selectride, afforded a 1:3 mixture of linear ketone (−)-**9** and hemiketal (−)-**10**, in 65% yield (three steps, Scheme 3). Gratifyingly, when the crude mixture was submitted to slow chromatography on silica gel, the linear intermediate was fully isomerized to the hemiketal to furnish (−)-**10** in 82% yield (three steps). All attempts to perform spiroketalization from the linear intermediate (−)-**9** were not met with success. Nevertheless, acidic treatment of (−)-**10** with CSA allowed cyclization to the thermodynamic spiroketal (−)-**11** in 88% yield. Interestingly, the use of PPTS for this step led to a separable mixture of the axial/axial spiroketal (−)-**11** and its equatorial/equatorial stereoisomer (−)-**12** (for conformational assignments, see Supporting Information) in a 3:2 ratio (62% yield). Variation on the nature of the acidic partner can therefore lead to different stereomeric 6,6-spiroketals. The primary alcohol of (−)-**11** was then selectively silylated to afford (−)-**13**. The structure of the spiroketal was assigned on the basis of its 2D NOESY ^{1}H NMR spectrum. The $^3J_{H,H}$ coupling constants observed for protons H−C(2″), H−C(3″), H−C(4″), H−C(8″), H−C(9″), and H−C(10″) as well as diagnostic NOEs [H−C(2″)/H−C(4″), H−C(8″)/H−C(10″)] established the chair conformation of the two rings. NOEs between the pairs of axial and equatorial H−C(5″)/H−C(11″) and cross-peaks between the signals of H−C(2″) and H−C(8″) proved the axial/axial conformation of the spiroketal.

The functionalities of the AB spiroketal of spongistatins were then introduced on the two rings (Scheme 4). Oxidation of the alcohol at C(4″) under Ley's conditions[11] followed by diastereoselective equatorial addition of methyl magne-

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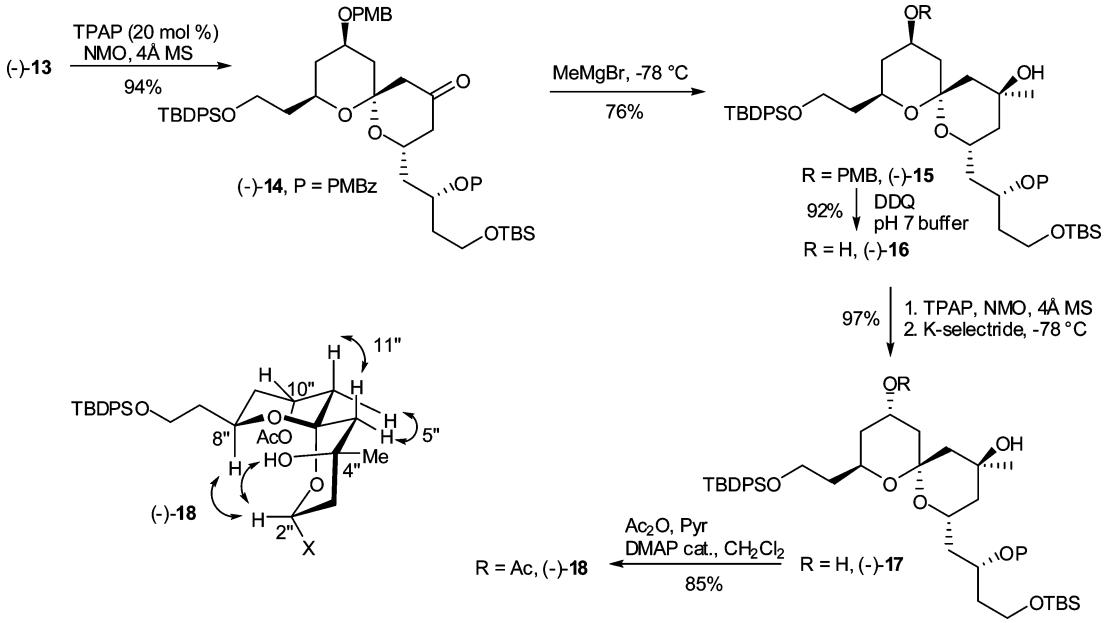
Scheme 4



sium bromide led to the tertiary alcohol (−)-**15**. The stereogenic center at C(10″) was installed by a sequence of smooth cleavage of the *p*-methoxybenzyl ether in the presence of DDQ, followed by oxidation of the resulting secondary alcohol. A diastereoselective reduction through equatorial addition of the hydride provided (−)-**17** as a single isomer and with a good yield (89%, three steps). A final selective acetylation furnished (−)-**18** which constitutes a very advanced precursor of the AB spiroketal of spongistatins.

The stereochemical assignments were confirmed through analysis of the 2D NOESY ^{1}H NMR spectrum of (−)-**18**. Diagnostic NOEs [H−C(2″)/HO−C(4″)] established the axial configuration of the tertiary alcohol at C(4″).

Cross-peaks between the signals of the pairs of axial and equatorial H−C(5″)/H−C(11″) as well as NOEs between the signals of H−C(2″) and H−C(8″) indicated that the axial/axial conformation of the spiroketal was maintained.

In summary, the synthesis of an advanced precursor of the AB spiroketal of spongistatins has been achieved from the previously reported diol **3**, with an 8% overall yield and through a sequence of highly diastereoselective transformations. This route requires the isolation of only 11 synthetic intermediates. Further studies toward the preparation of the CD spiroketal subunit are in progress in our laboratory. This versatile methodology should also give access to a number of analogues. Complete control of the chemoselective functional modifications is possible as the ester belonging to the cycloheptenyl moiety can be saponified more rapidly than those belonging to the acyclic side chain.

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Supporting Information Available: Experimental procedures and full analytical data (including ^{1}H, ^{13}C, and 2D spectra). This material is available free of charge via the Internet at http://pubs.acs.org.

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