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Synthesis of the C16–C28 Spiroketal Subunit of Spongistatin 1 (Altohyrtin A): The Pyrone Approach

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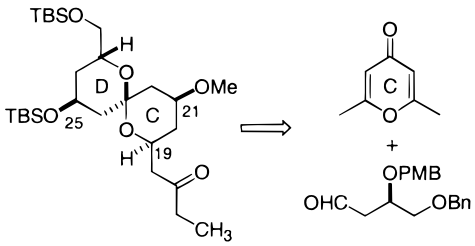
ABSTRACT



The synthesis of the CD spiroketal fragment of spongistatin 1 (altohyrtin A) has been accomplished utilizing the addition of a metalated pyrone to an aldehyde and subsequent acid-catalyzed spirocyclization. A stereoselective hydrogenation and subsequent conformational inversion establish the C19 stereocenter and the axial–equatorial spiroketal center.

The spongistatins,[1] altohyrtins,[2] and cinachyrolide A[3] are recently isolated members of a new class of antitumor agents.[4] We recently reported the preparation of the C1−C13 spiroketal (AB) subunit of the potent antitumor agent spongistatin 1[5] (altohyrtin A) **1**. Several other approaches to the AB spiroketal,[6] CD spiroketal,[6a,e,g,7] and EF fragments[8] have been reported, and recently the first total syntheses of altohyrtins A[9] and C[10] were described.

To date, most approaches to the CD spiroketal have relied on the thermodynamic equilibration of the anomeric center to control the spiroketal configuration. Since the CD spiroketal of spongistatin is an equatorial−axial spiroketal, thermodynamic control results in a mixture of the diaxial and equatorial−axial spiroketals in approximately equal ratios, depending on the reaction conditions. One exception is the apparent kinetic formation of a 6.5:1 ratio in favor of the axial−equatorial spiroketal observed by Heathcock.[6a]

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(3) Fusetani, N.; Shinoda, K.; Matsunoga, S. *J. Am. Chem. Soc.* **1993**, *115*, 3977−3981.

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As a result of the anticipated selectivity problems with thermodynamic control of the anomeric center, we sought a different approach to the CD spiroketal unit. A stereoselective hydrogenation of an unsaturated spiroketal **3** was chosen to kinetically establish the required axial−equatorial spiroketal configuration of the C16−C28 spiroketal subunit **2** (Figure 1). Enone **3** would be prepared through initial metalation of

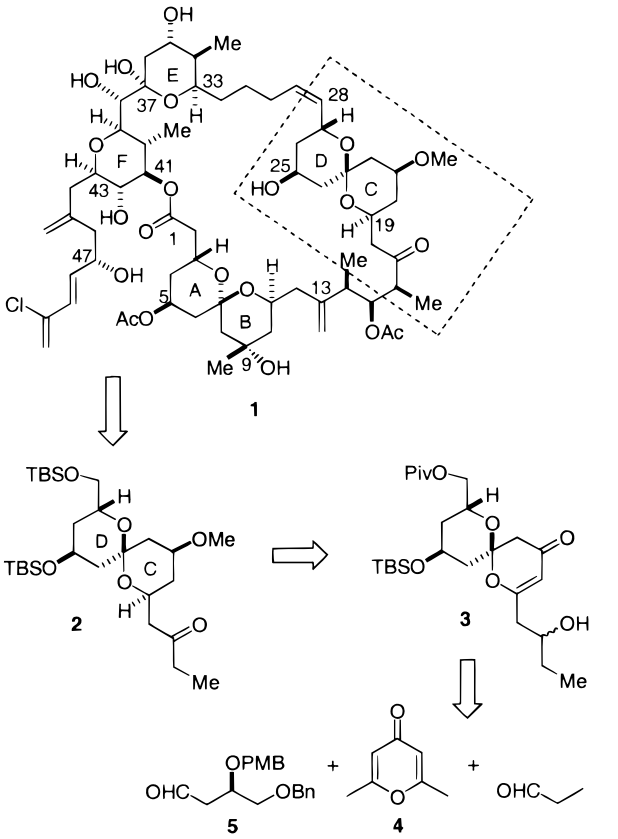
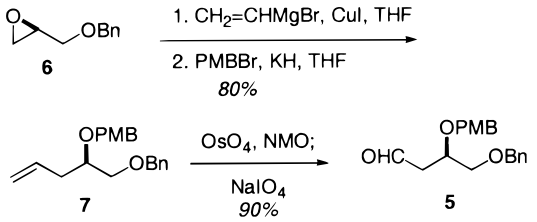


Figure 1. Retrosynthetic analysis.

pyrone **4** and sequential addition to aldehyde **5** and propionaldehyde. An acid-catalyzed cyclization[11] of the resultant hydroxypyrone would give the spiroenone **3**. The implementation of this strategy for the synthesis of the C16−C28 fragment of spongistatin 1 is reported here.

The synthesis began with the preparation of aldehyde **5** from commercially available (*S*)-benzyl glycidyl ether **6**, as illustrated in Scheme 1. Epoxide opening of **6** with vinylmagnesium bromide in the presence of CuI, followed by protection of the secondary alcohol as the *p*-methoxybenzyl ether, gave alkene **7** in excellent yield.[12] Oxidative cleavage of the alkene with osmium tetraoxide and sodium periodate produced 90% of the desired aldehyde **5**.

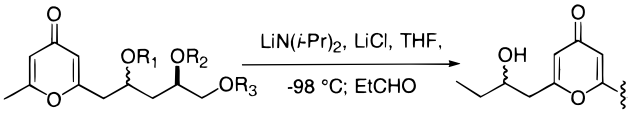
Scheme 1



With aldehyde **5** in hand, modification of 2,6-dimethyl-γ-pyrone **4**, which serves as the C ring of the spiroketal fragment, was initiated. Lithiation of 2,6-dimethyl-γ-pyrone **4** with lithium diisopropylamide and subsequent addition of aldehyde **5** produced pyrone aldol adduct **8** in 73% yield (Scheme 2). Protection of the secondary alcohol as the *tert*-butyldimethylsilyl ether followed by oxidative cleavage of the *p*-methoxybenzyl ether yielded hydroxypyrone **9** in 64% yield over two steps.

Elaboration of the other methyl group of pyrone **8** proved to be more challenging. A variety of metalation conditions on several differentially protected forms of pyrone **8** were surveyed. Most reaction conditions resulted in low conversion to the aldol adduct (about 20%) with a mass recovery of about 50%. During the course of these experiments, it was found that the mass recovery could be improved to 90% by utilizing LiCl as an additive and lowering the reaction temperature to −98 °C. Ultimately it was discovered that the presence of a free hydroxyl in the substrate, which resulted in the formation of a dianion, was important for acceptable conversions. As shown in Table 1, the only cases with yields over 30% were those where the pyrone contained a free hydroxyl on the side chain.

Table 1. Second Aldol Reactions on Pyrones



	R_1	R_2	R_3	Yield
9	TBS	H	Bn	63%
8	H	PMB	Bn	50%
	TBS	PMB	Bn	25%
	TBS	PMB	Piv	15%

(7) (a) Heathcock, C. H.; Hayes, C. J. *J. Org. Chem.* **1997**, *62*, 2678. (b) Paterson, I.; Wallace, D. J.; Gibson, K. R. *Tetrahedron Lett.* **1997**, *38*, 8911. (c) Paquette, L. A.; Braun, A. *Tetrahedron Lett.* **1997**, *38*, 5119−5122. (d) Smith, A. B., III; Zhuang, L.; Brook, C. S.; Lin, Q.; Moser, W. H.; Trout, R. E. L.; Boldi, A. *Tetrahedron Lett.* **1997**, *38*, 8671−8674.

(8) (a) Heathcock, C. H.; Ott, G. R. *Org. Lett.* **1999**, *1*, 1475. (b) Paterson, I.; Keown, L. E. *Tetrahedron Lett.* **1997**, *38*, 5727−5730. (c) Lemaire-Audoire, S.; Vogel, P. *Tetrahedron Lett.* **1998**, *39*, 1345−1348. (d) Smith, A. B., III; Zhuang, L.; Brook C. S.; Boldi, A.; McBriar, M. D.; Moser, W. H.; Murase, N.; Nakayama, K.; Verhoest, P. R.; Lin, Q. *Tetrahedron Lett.* **1997**, *38*, 8667−8670. (e) Hermitage, S. A.; Roberts, S. M.; Watson, D. J. *Tetrahedron Lett.*, **1998**, *39*, 3567. (f) Kary, P. D.; Roberts, S. M.; Watson, D. J. *Tetrahedron: Asymmetry* **1999**, *10*, 213. (g) Kary, P. D.; Roberts, S. M. *Tetrahedron: Asymmetry* **1999**, *10*, 217. (h) Fernandez-Megia, E.; Gourlaouen, N.; Ley, S. V.; Rowlands, G. J. *Synlett* **1998**, 991. (i) Micalizio, G. C.; Roush, W. R. *Tetrahedron Lett.* **1999**, *40*, 3351. (j) Dunkel, R.; Treu, J.; Hoffmann, H. M. R. *Tetrahedron: Asymmetry* **1999**, *10*, 1539.

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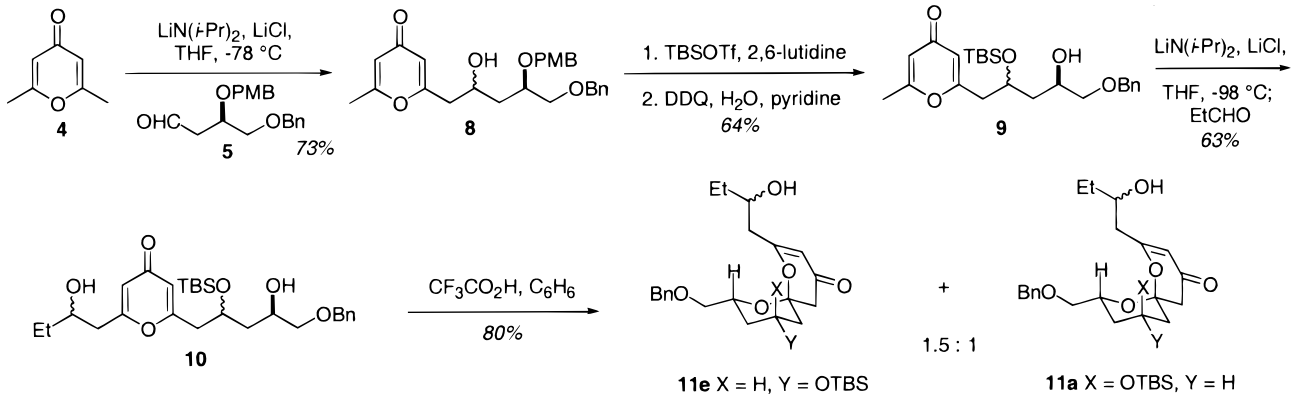
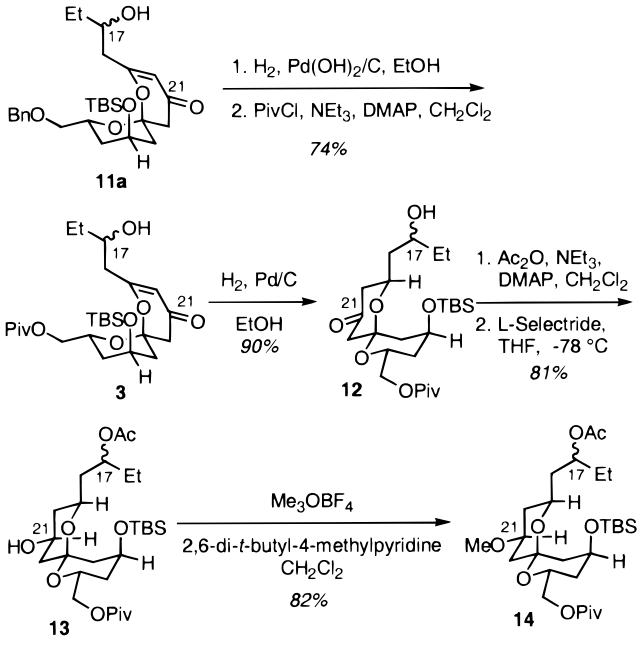
Scheme 2



Lithiation of hydroxypyrone **9** in the presence of LiCl and addition of excess propionaldehyde afforded dihydroxypyrone aldol adduct **10** in 63% yield. This mixture of diastereomers contains all of the required carbons for the C16−C28 fragment. Exposure of the mixture to catalytic trifluoroacetic acid in benzene afforded a 1:1.5 mixture of the spiroenones **11** and pyrone **10**. This mixture was readily separated by flash chromatography, and the spiroenone was ultimately obtained in greater than 80% yield after recycling.

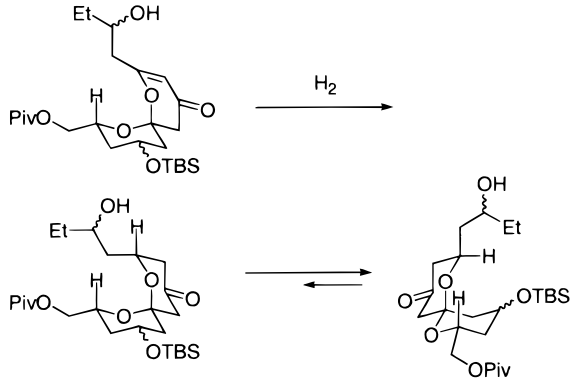
The benzyl ether of **11a** was then cleaved by hydrogenation over $Pd(OH)_2$, and the resulting primary alcohol was selectively protected as pivalate ester **3** in 74% yield over the two steps (Scheme 3). The spiroenone was hydrogenated

Scheme 3



over Pd/C, resulting in addition of hydrogen to the double bond solely from the equatorial face due to a combination of steric shielding by the pivaloate and the directing effect of the free hydroxyl. The resultant diaxially substituted C ring underwent ring inversion, as shown in Scheme 4, to

Scheme 4



provide axial−equatorial spiroketal **12** with the configuration required for the CD ring of spongistatin 1. The C17 hydroxyl was then protected as the acetate, and the ketone was stereoselectively reduced with L-Selectride to furnish alcohol **13**, which has all of the stereocenters required for the CD spiroketal ring. The C21 hydroxyl was converted to methyl ether **14** by treatment with Me_3OBF_4 and 2,6-di-*tert*-butyl-4-methylpyridine.

(10) (a) Evans, D. A.; Coleman, P. J.; Dias, L. C. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2738. (b) Evans, D. A.; Trotter, B. W.; Cote, B.; Coleman, P. J. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2741. (c) Evans, D. A.; Trotter, B. W.; Cote, B.; Coleman, P. J.; Dias, L. C.; Tyler, A. N. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2744. (d) Evans, D. A.; Trotter, B. W.; Coleman, P. J.; Cote, B.; Dias, L. C.; Rajapakse, H. A.; Tyler, A. N. *Tetrahedron* **1999**, *55*, 8671−8726.

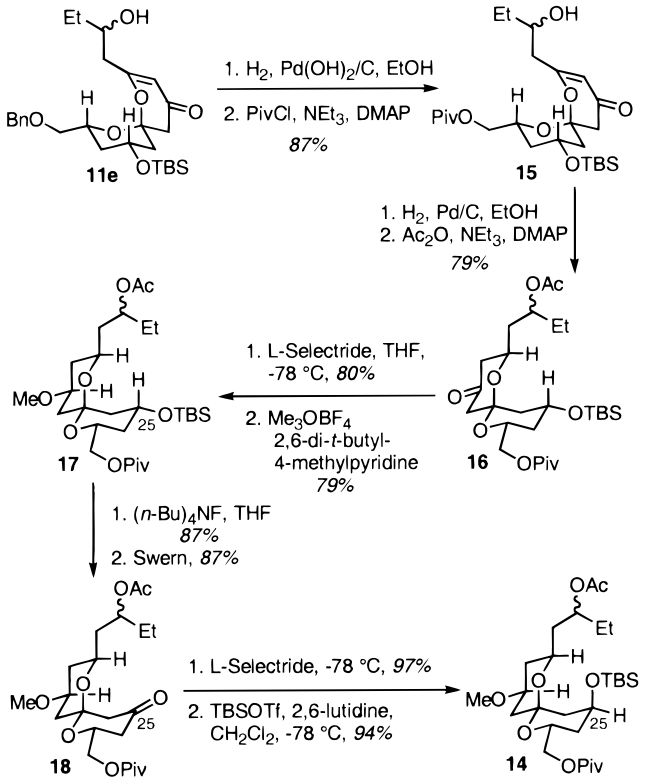
(11) (a) Crimmins, M. T.; O′Mahony, R.; *J. Org. Chem.* **1990**, *55*, 5894−5900. (b) Crimmins, M. T.; Washburn, D. G.; Katz, J. D.; Zawacki, F. J. *Tetrahedron Lett.* **1998**, *39*, 3439−3442.

(12) All new compounds were characterized by ^1H and ^{13}C NMR, IR, and optical rotation. Yields are for isolated, chromatographically purified products.

(13) Mancuso, A. J.; Huang, S. L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.

The equatorial isomer of the spiroketalization, **11e**, was also readily converted to **14**, as shown in Scheme 5. The

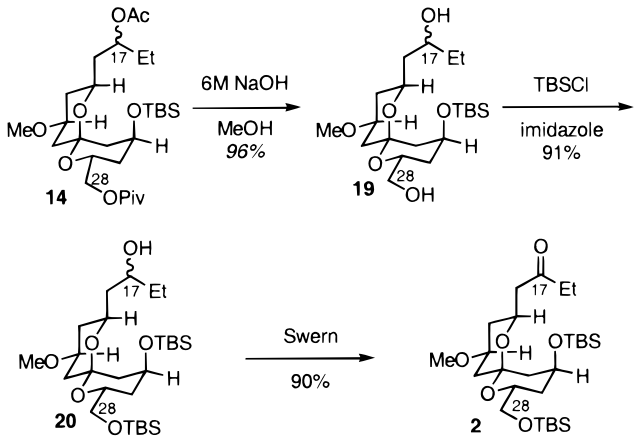
Scheme 5



benzyl ether was converted to pivalate ester **15** as above, and the enone was reduced via a catalytic hydrogenation followed by hydroxyl protection to furnish acetate **16**. Stereoselective reduction of the ketone, and conversion to the methyl ether, provided spiroketal **17**. The C25 silyl ether was then cleaved using tetrabutylammonium fluoride, and the resulting secondary alcohol was oxidized under Swern[13] conditions to produce ketone **18**. The ketone was stereoselectively reduced with L-Selectride to the axial alcohol, which was converted to *tert*-butyldimethylsilyl ether **14** in 94% yield upon treatment with TBSOTf and 2,6-lutidine at −78 °C, thereby completing inversion of the C25 stereocenter. This inverted material could then be combined with the previously synthesized **14** and carried on to complete the CD fragment.

Completion of the CD spiroketal from **14** required only adjustment of the oxidation state at C17 and a change of the C28 protecting group. Hydrolysis of both the acetate and pivaloate esters with sodium hydroxide in methanol afforded diol **19** in 96% yield (Scheme 6). Selective protection of the primary hydroxyl as the *tert*-butyldimethylsilyl ether and oxidation of the secondary hydroxyl to the ketone under Swern conditions accessed the fully functionalized C16−C28 spiroketal fragment **2** in 82% yield over the two steps.

Scheme 6



Support for the stereochemical assignment of the final product, **2**, was obtained by inspection of the NOESY spectrum (Figure 2). A strong NOE was observed between

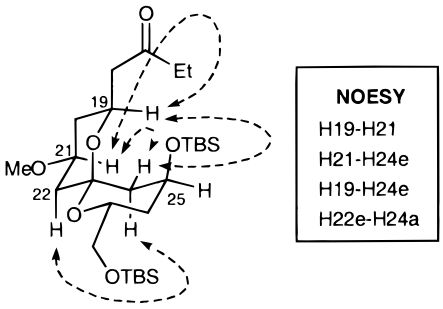


Figure 2.

the C19 and C21 axial protons, as well as between the C19 axial proton and C24 equatorial proton and the C21 axial proton and C24 equatorial proton. This C19−C21−C24 triad as well as the C22eq−C24ax interaction is diagnostic in spongistatin 1 as well. The C27 proton was assigned as axial on the basis of its coupling constants to C26, and similarly, the equatorial nature of C25 was assigned by its coupling constants with the C24 and C26 hydrogens.

The C16−C28 axial−equatorial spiroketal fragment of spongistatin 1 has been prepared in a highly stereoselective manner from 2,6-dimethyl-γ-pyrone and (*S*)-benzyl glycidyl ether. Efforts are underway to connect the AB and CD spiroketal fragments and complete the synthesis of spongistatin 1.

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Supporting Information Available: Experimental procedures and full characterization for compounds **2**, **3**, **5**, and **7**−**20**. This material is available free of charge via the Internet at http://pubs.acs.org.

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