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SYNTHETIC STUDIES TOWARDS HALICHONDRINS

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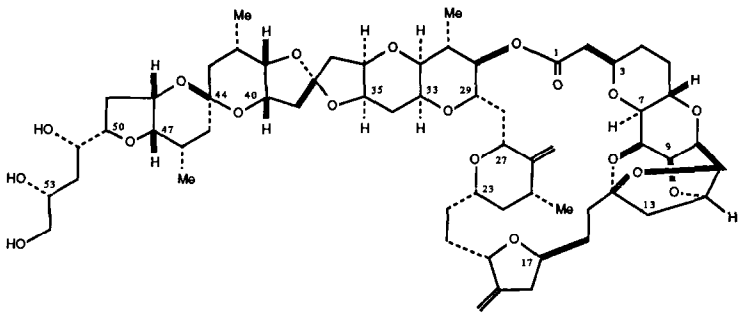
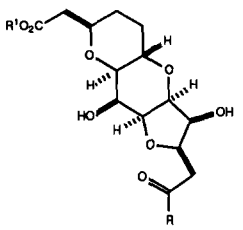
Abstract: An efficient, stereocontrolled route to construct the polycyclic ring system found at the C.1-C.15 moiety of halichondrins is reported.

Hirata, Uemura, and co-workers have recently reported the successful isolation and structure elucidation of halichondrins, antitumor polyether macrolides isolated from a marine sponge.[1] We were intrigued by the complex ring systems, particularly the polycyclic ring system around the C.1-C.15 moiety, cf. halichondrin B (1). In this communication, we would like to report an efficient, stereocontrolled route to construct such a ring system.

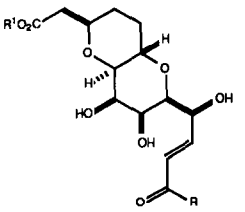


1: Halichondrin B

From the synthetic point of view, this ring system should be equivalent with the dihydroxy ketone 2. We hoped that 2 would be accessible from the α,β-unsaturated ketone 3 or the α,β-acetylenic ketone 4, both of which could be synthesized by using the $NiCl_2/CrCl_2$-mediated coupling[2] of the aldehyde 5 with suitable iodides.

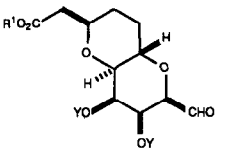


2



3

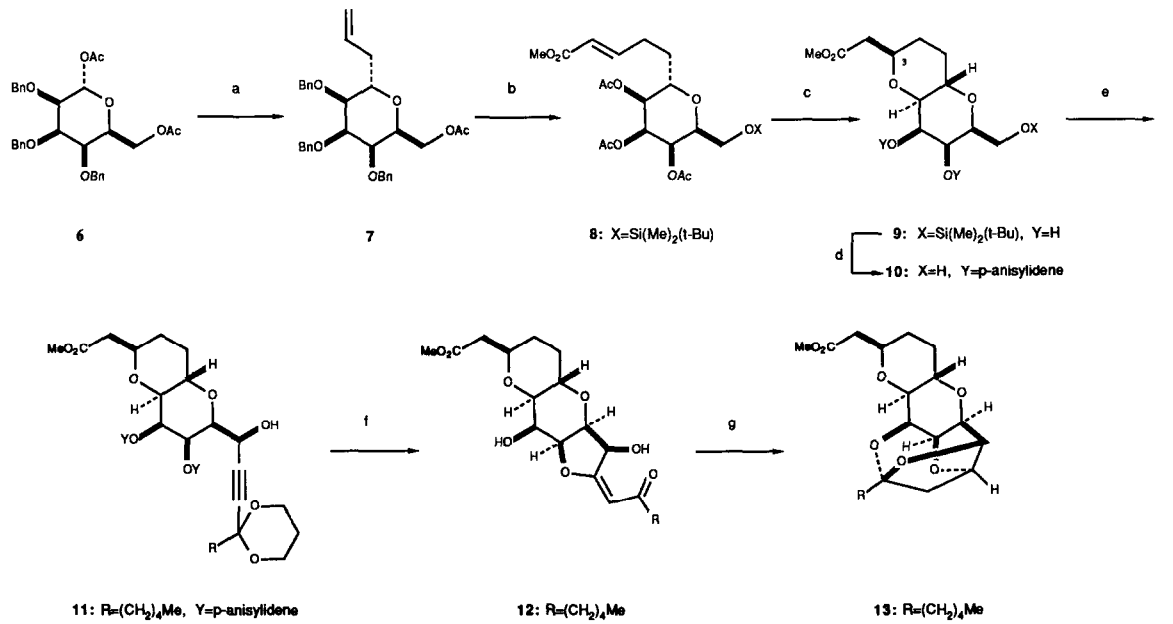
4: α,β-acetylenic ketone instead of α,β-unsatuated ketone in 3



5

Our synthesis started with the diacetate 6,[3,4] readily prepared from 1,6-anhydro-D-galactose 3,4-acetonide.[5] The stereocontrolled C-glycosidation[6] of 6 yielded the desired axial product 7 in 83% yield (the stereoselectivity: >100:1). Application of routine synthetic operations allowed us to transform 7 into the trans-α,β-unsaturated ester 8 in 53% overall yield. After hydrolysis of the acetyl groups, 8 was treated with Triton B to effect the Michael addition. The desired bicyclic ester 9 was isolated in 89% overall yield as a 2.8:1 diastereomeric mixture. Although this ratio did not appear to be a reflection of the thermodynamical stability of these two diastereomers, attempted epimerization at the C.3 position under basic conditions was very sluggish. However, this problem was solved through formation of the C.8-C.9 p-anisylidene, followed by brief exposure to base, to provide an approximately 50:1 ratio of the desired C.3-diastereomer over its epimer.[7] Thus, for practical purposes, the transformation of 8 into 10 was most conveniently achieved without isolation of the intermediates in 75% overall yield.

Scheme



Reagents and Conditions

a. CH_2=$CHCH_2Si(Me)_3/BF_3 \cdot Et_2O/0°C$.[6]

b. 1. $LiAlH_4/Et_2O/0°C$. 2. (t-Bu)$(Me)_2SiCl/DMAP/py/CH_2Cl_2/40°C$. 3. Li/liq. $NH_3/THF/-78°C$. 4. $Ac_2O/DMAP/py/50°C$. 5. $BH_3 \cdot (Me)_2S/EtOAc$-THF (1:15)/0°C, followed by H_2O_2/aq. NaOH work-up. 6. Swern oxidation.[14] 7. $(Ph)_3P$=$CHCO_2Me/CH_2Cl_2/0°C$.

c. NaOMe/MeOAc-MeOH (4:1000)/0°C, followed by Triton B treatment (Triton B/MeOH/0°C->RT).

d. 1. p-MeOPhCH$(OMe)_2$/PPTS/molecular sieves/C_6H_6/RT. 2. Triton B/C_6H_6/RT. 3. (n-Bu)$_4$NF/THF/0°C

e. 1. Swern oxidation.[14] 2. I-C≡CR'/$NiCl_2$ (0.01%)-$CrCl_2$/THF/RT.[2,9]

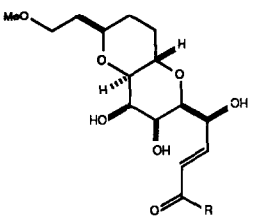
f. 48% HF-CH_3CN (1:20)/RT, followed by $NaHCO_3$ work-up and then filtered through a short silica gel column.

g. 1. $H_2/Pd(OH)_2$ on C/Et_2O/RT. 2. PPTS/MeOH-CH_2Cl_2 (1:20)/RT.[10]

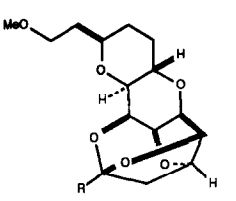
After Swern oxidation, 10 was subjected to the $NiCl_2/CrCl_2$-mediated coupling reaction with $I\text{-}C{\equiv}CC(OR)_2(CH_2)_4Me$ (1.4 equiv), to yield the propargyl alcohol 11 with the desired configuration in 58% yield along with its stereoisomer (7%). This coupling reaction deserves several comments. First, as we described before,[8] this procedure is exceptionally well suited for the case where the aldehyde is labile. In the present case, the aldehyde can potentially give problems associated with enolization, such as epimerization and dehydration. However, under the $NiCl_2/CrCl_2$-mediated coupling conditions, no complication was observed. Second, the stereoselectivity was approximately 8.3:1, favoring the desired, anticipated[8] diastereomer. Third, the $NiCl_2$-content in $CrCl_2$ needs to be much lower for iodoacetylenes[9] than that for iodoolefins.

Acid-treatment of 11 effected a series of reactions, i.e. hydrolysis of the ketal and anisylidene groups and Michael addition, to furnish the labile enone 12. The ring system of 12 provided an opportunity to stereoselectively introduce the C.12 asymmetric center; indeed, hydrogenation of 12 took place exclusively from the anticipated convex face. Upon treatment with pyridinium p-toluenesulfonate (PPTS)[10,11] this substance spontaneously cyclized to the desired product 13 in 80% yield. The spectroscopic data (^{1}H-NMR, ^{13}C-NMR, MS, IR) were completely consistent with the structure 13; especially the ^{1}H-NMR signals of 13 correspond extremely well to those of halichondrins reported in the literature.[12]

As mentioned, the desired ring system could in principle be constructed by acid-catalyzed intramolecular ketalization of 3 as well. In this connection, it is interesting to note that the desired polycyclic product 15 was isolated in 65% yield upon acid-treatment [PPTS/MeOH-CH_2Cl_2 (1:20)/RT] of 14.[13]



14: R=$(CH_2)_4$Me



15: R=$(CH_2)_4$Me

Acknowledgement: Financial support from the National Institute of Health (CA-22215) is gratefully acknowledged.

References and Footnotes

1. (a) Uemura, D.; Takahashi, K.; Yamamoto, T.; Katayama, C.; Tanaka, J.; Okumura, Y.; Hirata, Y. J. Am. Chem. Soc. 1985, 107, 4796. (b) Hirata, Y.; Uemura, D. Pure Appl. Chem. 1986, 58, 701.
2. (a) Jin, H.; Uenishi, J.; Christ, W. J.; Kishi, Y. J. Am. Chem Soc. 1986, 108, 5644. (b) Takai, K.; Tagashira, M.; Kuroda, T.; Oshima, K.; Utimoto, K.; Nozaki, H. J. Am. Chem. Soc. 1986, 108, 6048.
3. The substances reported in this paper belong to the antipodes of halichondrins. The drawings are, however, made in the same absolute configurations as that of halichondrins.

4. Satisfactory spectroscopic data were obtained for all the new compounds reported in this paper.
5. The diacetate 6 was prepared from 1,6-anhydro-D-galactose 3,4-acetonide in 80% overall yield in 5 steps, 1. Swern oxidation[14], 2. $NaBH_4$/EtOH-H_2O(1:1)/0°C, 3. AcOH-H_2O (4:1)/80°C, 4. $PhCH_2Br$/NaH/(n-Bu)$_4NI$/DMF/RT, and 5. $Ac_2O/BF_3 \cdot Et_2O$/RT. Transformation of 1,6-anhydro-D-galactose 3,4-acetonide into 1,6-anhydro-D-talose 3,4-acetonide is known: Hughes, N. A. Carbohydr. Res. 1968, 7, 474. For a review on 1,6-anhydrosugars, see Cerny, M.; Stanek, J. Jr. Adv. Carbohydr. Chem. Biochem. 1977, 34, 23.
6. Lewis, M. D.; Cha, J. K.; Kishi, Y. J. Am. Chem. Soc. 1982, 104, 4976. For a recent paper on this subject, see Giannis, A.; Sandhoff, K. Tetrahedron Lett. 1985, 26, 1479 and references cited therein.
7. With respect to the anisylidene moiety, a single stereoisomer was formed.
8. Kishi, Y.; Christ, W. J.; Taniguchi, M. "Natural Products and Biological Activities", eds Imura, H.; Goto, T.; Murachi, T.; Nakajima, T. University of Tokyo Press, 1986, pp 87-98.
9. For other examples, see: Takai, K.; Kuroda, T.; Nakatsukasa, S.; Oshima, K.; Nozaki, H. Tetrahedron Lett. 1985, 26, 5585.
10. Miyashita, M.; Yoshikoshi, A.; Grieco, P. A. J. Org. Chem. 1977, 42, 3772.
11. This cyclization was also effected on silica gel.
12. The ^1H-NMR data of halichondrin B[1b] are well compared with those of 13:

Proton	Halichondrin B (360 MHz, CD_3OD)	Compound 13 (500 MHz, CD_3OD)
2	2.44 (dd, J=16.5, 3.0)	2.45 (dd, J=15.8, 5.1)
2'	2.57 (dd, J=16.5, 9.3)	2.52 (dd, J=15.8, 7.6)
3	3.88 (m)	3.81 (m)
4	1.35	1.40 (m)
4'	1.75	1.80 (m)
5	1.41	1.40 (m)
5'	2.04	2.05 (m)
6	4.33 (ddd, J=9.3, 9.3, 4.0)	4.29 (ddd, J=10.0, 9.6, 4.3)
7	2.98 (dd, J=9.3, 2.4)	2.96 (dd, J=9.6, 1.9)
8	4.31 (dd, J=3.6, 2.4)	4.33 (dd, J=4.1, 1.9)
9	4.13 (dd, J=6.0, 3.6)	4.11 (dd, J=6.6, 4.1)
10	4.18 (dd, J=6.0, 4.5)	4.17 (dd, J=6.6, 4.6)
11	4.60 (dd, J=4.5, 4.5)	4.58 (dd, J=4.6, 4.4)
12	4.71 (dd, J=4.5, 4.5)	4.67 (dd, J=4.7, 4.4)
13	1.98 (dd, J=12.6, 4.5)	1.98 (dd, J=13.3, 4.7)
13'	2.09 (d, J=12.6)	2.03 (d, J=13.3)

13. Attempted cyclization of the methyl ester corresponding to 14 did not yield promising results.
14. (a) Omura, K.; Swern, D. Tetrahedron 1978, 34, 1651. (b) Mancuso, A. J.; Huang, S.-L; Swern, D. J. Org. Chem. 1978, 43, 2480.

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