Tetrahedron Letters,Vol.23,No.13,pp 1319-1322,1982 0040-4039/82/131319-04$03.00/0
Printed in Great Britain

SIRODESMIN A: SYNTHESIS OF A CHIRAL LEFT HALF.

William H. Rastetter[1,*] and Julian Adams
Department of Chemistry, Massachusetts Institute of Technology,
Cambridge, Massachusetts 02139

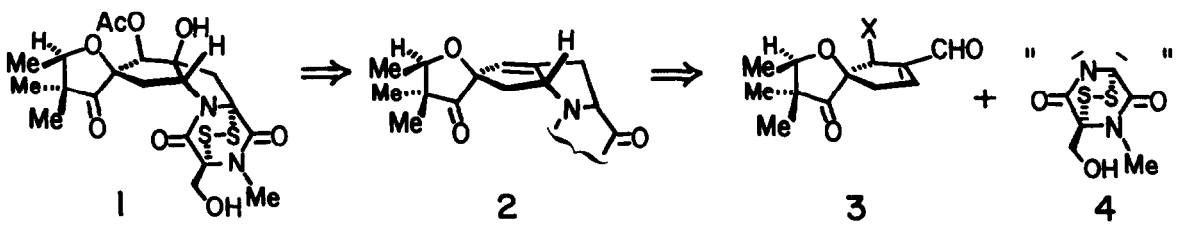
Jon Bordner
Department of Chemistry, North Carolina State University,
Raleigh, North Carolina 27650

Abstract: A stereoselective and chiral synthesis of a precursor to the fungal metabolite sirodesmin A (1) is described. The correct relative and absolute configuration for intermediate 3 (Scheme 1) is established in a single, highly enantioselective epoxidation.

We have been attracted to the sirodesmins[2] as synthetic targets owing to their diversity of heteroatom functionality, spiro-fused rings and complex stereochemistry. Herein we outline an approach to α,β-unsaturated aldehyde 3 (Schemes 1 and 2), a chiral precursor of the fungal metabolite, sirodesmin A (1). The correct relative and absolute configuration for 3 is established in a single, highly enantioselective step.

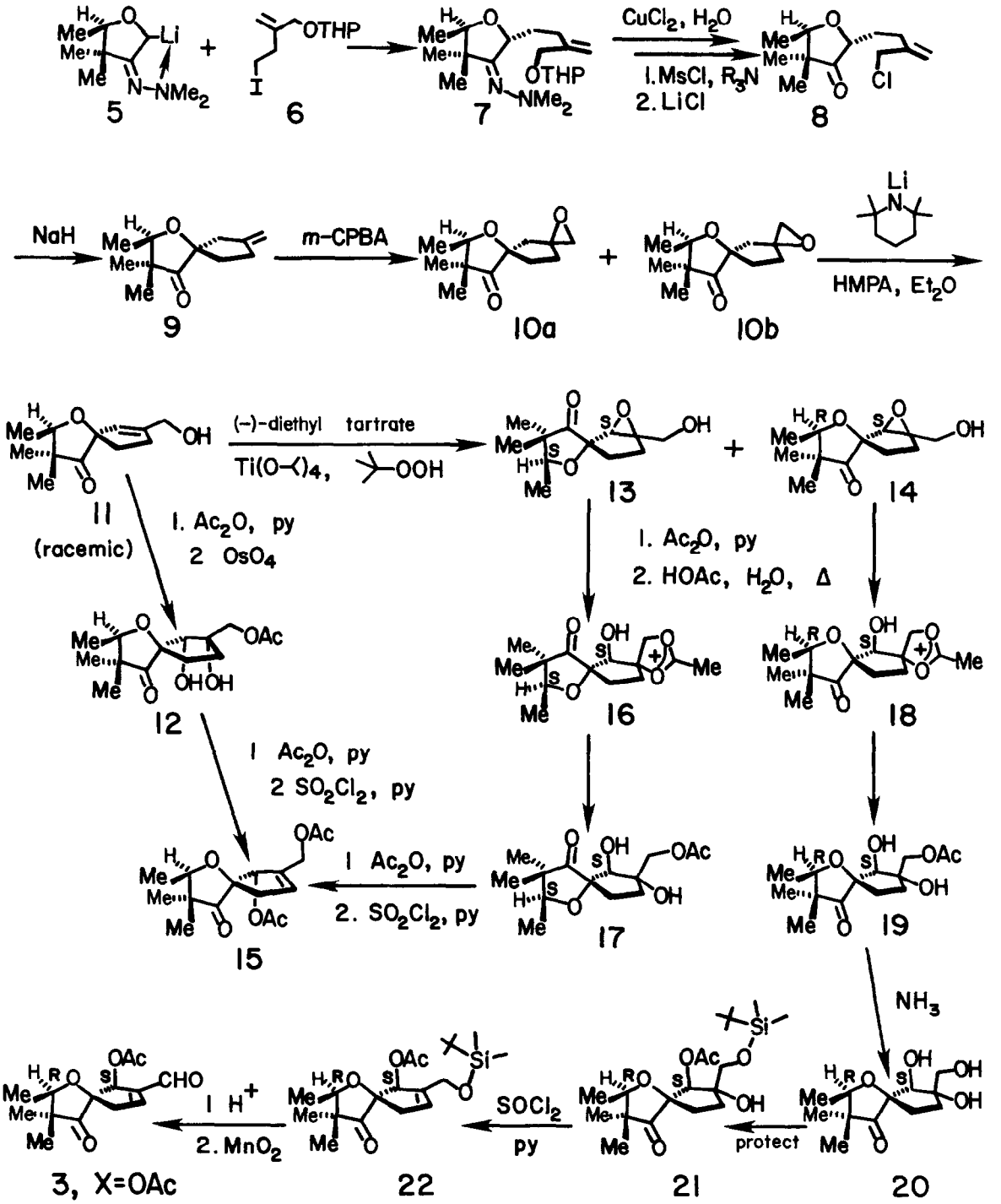
Retrosynthetic analysis (Scheme 1) suggests olefin 2 as a precursor to sirodesmin A (1). cis-Hydroxylation of 2 from the top face (as drawn) would provide the cis-fusion of five-membered rings[3] seen in the target (1). Dissection of 2 reveals pieces 3 (see also Scheme 2) and 4 as smaller precursors. A synthon developed by Kishi and coworkers[4] for their syntheses of gliotoxin and related metabolites should be directly applicable to the right half of sirodesmin A, represented formally as dianion 4. In the synthetic direction, conjugate addition by the nitrogen of 4 to 3 with expulsion of the leaving group X would join the synthetic intermediates. Aldehyde reduction and ring closure would complete the assembly of olefin 2.

Scheme I



Our approach to chiral precursor 3 is shown in detail in Scheme 2. Stereoselective alkylation of racemic metallohydrazone 5[5,6] by homoallylic iodide 6[7] affords allylic THP ether 7

Scheme 2


5
6
7
8
9
10a
10b
11
(racemic)
12
13
14
15
16
17
18
19
20
21
22
3, X=OAc
CuCl2, H2O
1. MsCl, R3N
2. LiCl
NaH
m-CPBA
HMPA, Et2O
(−)-diethyl tartrate
Ti(O-i-Pr)4,
t-BuOOH
1. Ac2O, py
2 OsO4
1. Ac2O, py
2. HOAc, H2O, Δ
1 Ac2O, py
2 SO2Cl2, py
1 Ac2O, py
2. SO2Cl2, py
NH3
protect
SOCl2
py
1 H+
2. MnO2

(83%). Hydrolysis of the tetrahydropyranyl ether and of the hydrazone is effected by aqueous Cu(II)[6c]. Spiro-annulation is achieved via allylic chloride 8 (75% from 7). The highly stereoselective alkylation, 8 → 9[8] (90%), is attributed to the approach of the allylic chloride to the enolate face opposite the cis-vicinal furanone methyl groups. Epoxidation of 9 yields a 1:1 mixture of epoxides, 10a,b (95%), which without separation is rearranged to racemic allylic alcohol 11[9] (54%). The structure of 11 is firmly established by single crystal X-ray structure analysis of the derived acetate diol 12.[10]

Neither cis-hydroxylation (OsO_4)[10] nor peracid epoxidation of 11 proceed stereoselectively. Nonetheless, stereoselective functionalization and resolution of racemate 11 can be accomplished in a single synthetic operation. Epoxidation of 11 using the Sharpless chiral tartrate strategy[11] affords diastereomeric epoxy ketones 13 and 14 in high chemical (90%) and optical (>95%)[12] yields. Thus, the S-configured half of racemic furanone 11 is converted into the syn-epoxy ketone (13)[13] and the R-configured half into the anti-epoxy ketone (14).[13] The latter intermediate (14) displays the correct absolute configuration for sirodesmin A (see 1 and 3, Scheme 1).

Structure assignment to separated[14] epoxy ketones 13 and 14 is achieved by correlating the syn-epoxy ketone (13) with 12 in which the syn-relationship of diol and ketone is known from X-ray analysis. Acetylation and dehydration of 12 yields racemic diacetate olefin 15. Acetylation and epoxide hydration of 13 yields diol acetate 17; acetylation and dehydration, in turn, yield chiral diacetate olefin 15. Exciton chirality assignment of configuration to diol acetate 17[15] confirms the indicated configuration (S) of the secondary alcohol. Thus, the configuration of epoxide 13 at the secondary carbon is retained during the hydrolysis reaction which likely proceeds via the spiro-fused acetoxonium cation 16.

Acetylation and hydrolysis of 14 proceeds, presumably via cation 18, affording diol acetate 19 contaminated by triol 20. The mixture is converted into pure triol (20, 81% from 14) by aminolysis, then protected by sequential silylation (60%) and acetylation (81%). Dehydration of tertiary alcohol 21 provides olefin silyl ether 22 (92%); deprotection and oxidation yields the desired chiral intermediate 3 (quantitative from 22).

The steps required to complete a total synthesis of sirodesmin A (1), shown retrosynthetically in Scheme 1, are being explored in a model α,β-unsaturated aldehyde lacking the furanone (see 3).[16] The model aldehyde has been joined efficiently via Michael addition[16] to the Kishi synthon.[4] In due course, we hope to report the completed synthesis of sirodesmin A (1).[17]

Acknowledgment. We thank Mr. D. Conatser and Drs. A. Basak and R. Wattley for technical assistance and for their continuing efforts on this project. Funding was generously provided by the National Science Foundation. We are grateful to Dr. C. Costello for exact mass measurements.

References and Notes.

(1) Alfred P. Sloan Fellow, 1980-1982.

(2) (a) P. J. Curtis, D. Greatbanks, B. Hesp, A. F. Cameron, A. A. Freer, J. Chem. Soc., Perkin Trans. 1 1977, 180. (b) J. P. Férézou, C. Riche, A. Quesneau-Thierry, C. Pascard-Billy, M. Barbier, J. F. Bousquet, G. Boudart, Nouv. J. Chim. 1977, 1, 327. (c) J. P. Férézou, A. Quesneau-Thierry, M. Barbier, A. Kollmann, J. F. Bousquet, J. Chem. Soc., Perkin Trans 1 1980, 113.

(3) Approach of the cis-hydroxylating reagent (OsO_4) from the more hindered bottom face would provide the more strained trans-fusion of five-membered rings.

(4) See for example (a) Y. Kishi, T. Fukuyama, S. Nakatsuka, J. Amer. Chem. Soc. 1973, 95, 6490. (b) T. Fukuyama, Y. Kishi, ibid, 1976, 98, 6723.

(5) The parent furanone was reported by P. Yates, A. K. Verma, J. C. L. Tam, Chem. Commun. 1976, 933. We thank Professor Yates for full experimental details for the preparation of the furanone.

(6) For use of N,N,-dimethylhydrazones in synthesis see. (a) E. J. Corey, D. Enders, Tetrahedron Lett. 1976, 3 and 11. (b) E. J. Corey, D. Enders, M. G. Bock, ibid, 1976, 7. (c) E. J. Corey, S. Knapp, ibid, 1976, 3667.

(7) Prepared from 3-methyl-3-buten-1-ol; full experimental details for the preparation of 6 will be reported in a subsequent paper

(8) A minor isomer (<5% by high field ^1H and ^{13}C NMR) is formed in the spiro-annulation.

(9) A single allylic alcohol (11) is formed by rearrangement of 10a,b. The rearrangement may be directed through coordination of the lithium amide to the furanone or by stereoelectronic and inductive effects.

(10) syn-Keto diol 12 (1.7 parts) is formed along with the diastereomeric, anti-keto diol (not shown, 1.0 part).

(11) T. Katsuki, K. B. Sharpless, J. Am. Chem. Soc. 1980, 102, 5974.

(12) The optical yields for 13 and 14 are too high to be determined by high field ^1H NMR spectroscopy of the derived Mosher esters; see: J. A. Dale, D. L. Dull, H. S. Mosher, J. Org. Chem. 1969, 34, 2543. Racemic 13 and 14 were used as standards.

(13) The epoxide configuration for 13 and 14 is determined by the chirality of the unnatural, (-)-diethyl tartrate ligand; see ref. 11.

(14) Epoxy ketones 13 (R_f = 0.2) and 14 (R_f = 0.3) are separated by silica gel chromatography (1:1 hexanes, EtOAc).

(15) To assign configuration to 17, the secondary alcohol was benzoylated and the tertiary alcohol was dehydrated (SO_2Cl_2, py; compare 17 → 15). The derived, secondary allylic benzoate shows a positive benzoate Cotton effect indicative of the S configuration for 17; see: N. Harada, J. Iwabuchi, Y. Yokota, H. Uda, K. Nakanishi, J. Am. Chem. Soc. 1981, 103, 5590.

(16) Dan Conatser, unpublished work from our laboratory.

(17) All intermediates reported herein display satisfactory spectral data. Satisfactory combustion analysis (C, H, I) was obtained for iodide 6; elemental composition was verified by exact mass measurements for the hydrazone precursor to 5 (M^+), allylic chloride 8 (M^+), olefin 9 (M^+), the acetate derivative of 11 (M^+), triol 20 (M^+), acetate 22 ($M^+ - C_4H_9$; M^+ absent) and aldehyde 3 ($M^+ - C_2H_2O$, weak M^+ detected).

(Received in USA 30 November 1981)