We also found that the coupling reaction proceeds in the presence of a catalytic amount of I. For example, irradiation with ultrasound to a mixture of finely powdered 1 and a 0.2 molar amount of I at 50 °C for 24 h gave 4 in 89% yield. This result shows that oxidation of Fe^{2+} to Fe^{3+} under the air occurs easily in the solid state.

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Synthesis of the C(1)-C(15) Segment of Streptovaricin D

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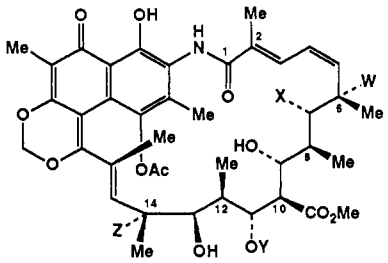
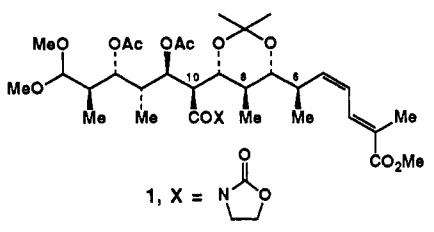
Summary: A highly stereoselective synthesis of the C(1)-C(15) segment (1) of streptovaricin D is reported.

Sir: The streptovaricins are a group of biologically active ansamycin antibiotics isolated from *Streptomyces spectabilis*.[1] The stereochemistry of streptovaricin C was assigned by X-ray structure determination of a crystalline derivative,[2] while assignments for the other streptovaricins are based on chemical and biosynthetic interconversions.[1,3] We have initiated work on the total synthesis of streptovaricin D (SvD), the simplest member of this group and also a biosynthetic precursor of the others,[3] and report here a highly stereoselective synthesis of the C(1)-C(15) segment (1) corresponding to the ansa chain of SvD.[4]



Streptovaricin	W	X	Y	Z
A	OH	OH	OAc	OH
B	H	OH	OAc	OH
C	H	OH	H	OH
D	H	OH	H	H
E	H	O=	H	OH
G	OH	OH	H	OH
J	H	OAc	H	OH
K	OH	OAc	H	OH



A significant problem associated with the synthesis of the streptovaricins concerns the introduction of the branching C(10)-CO_2Me group. After consideration of several possibilities we decided to adopt the Evans aldol procedure using chiral crotonate imide **3a**[5] for the conversion of aldehyde **2**[6] to intermediate **4**. The acyloxazolidone unit of 4 would function as a precursor to the branching CO_2Me group of 1, while the vinyl appendage would serve as the point of further chain elongation via the kinetically nonacidic aldehyde **6**.[7] In the event, aldehyde **2** was smoothly elaborated to **4a** (only one isomer detected) by using the Evans asymmetric aldol technology (Scheme I). We subsequently found, however, that double asymmetric synthesis[8] was not required to achieve high diastereoselectivity in this aldol reaction as use of the boron enolate derived from the achiral crotonate imide **3b** provided **4b** with 95:5 diastereoselectivity (84% isolated yield). Aldol **4b** was smoothly elaborated to the acetonide derivative **5b** by hydrolysis of the TES ether followed by treatment of the resulting diol with 2,2-dimethoxypropane and catalytic pTsOH. The stereochemistry of **5b** was verified by reduction with $NaBH_4$ in MeOH and acylation of the primary alcohol to give an acetate derivative that correlated exactly with the primary acetate similarly prepared from **5a**.[9]

Ozonolysis of **5b** provided the potentially sensitive aldehyde **6b** that was used without purification in subsequent crotylmetalation experiments. The most selective

†Holder of an ACS Organic Division Fellowship sponsored by Eli Lilly, 1987-88.

(1) Rinehart, K. L., Jr.; Shield, L. S. *Fortschr. Chem. Org. Naturst.* **1976**, *33*, 231.

(2) Wang, A. H.-J.; Paul, I. C.; Rinehart, K. L., Jr.; Antosz, F. J. *J. Am. Chem. Soc.* **1971**, *93*, 6275. The stereochemistry at C(6) and C(7) of streptovaricin C is drawn incorrectly in the two-dimensional structure reported in this paper. The stereoscopic views, however, depict the actual stereochemistry. Correct stereochemical representations also appear in ref 1.

(3) (a) Deshmukh, P. V.; Kakinuma, K.; Ameel, J. J.; Rinehart, K. L., Jr.; Wiley, P. F.; Li, L. H. *J. Am. Chem. Soc.* **1976**, *98*, 870. (b) Rinehart, K. L., Jr.; Antosz, F. J.; Deshmukh, P. V.; Kakinuma, K.; Martin, P. K.; Mulavetz, B. I.; Sasaki, K.; Witty, T. R.; Li, L. H.; Reusser, F. *J. Antibiot.* **1976**, *29*, 201.

(4) For previous synthetic studies on the streptovaricins: (a) McCarthy, P. A. *Tetrahedron Lett.* **1982**, *23*, 4199. (b) Trost, B. M.; Pearson, W. H. *Tetrahedron Lett.* **1983**, *24*, 267. (c) Fraser-Reid, B.; Magdzinski, L.; Molino, B. F.; Mootoo, D. R. *J. Org. Chem.* **1987**, *52*, 4495. (d) Fraser-Reid, B.; Molino, B. F.; Magdzinski, L.; Mootoo, D. R. *Ibid.* **1987**, *52*, 4505. (e) Mootoo, D. R.; Fraser-Reid, B. *Ibid.* **1987**, *52*, 4511. (f) McCarthy, P. A.; Kageyama, M. *Ibid.* **1987**, *52*, 4681. (g) Schreiber, S. L.; Wang, Z.; Schulte, G. *Tetrahedron Lett.* **1988**, *29*, 4085.

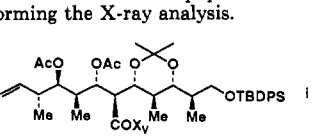
(5) Evans, D. A.; Sjogren, E. B.; Bartroli, J.; Dow, R. L. *Tetrahedron Lett.* **1986**, *27*, 4957.

(6) Aldehyde **2** is the enantiomer of the intermediate in our synthesis of the rifamycin ansa chain: Roush, W. R.; Palkowitz, A. D. *J. Am. Chem. Soc.* **1987**, *109*, 953.

(7) (a) Evans, D. A.; Ennis, M. D.; Le, T.; Mandel, N.; Mandel, G. *J. Am. Chem. Soc.* **1984**, *106*, 1154. (b) Evans, D. A.; Sjogren, E. B. *Tetrahedron Lett.* **1986**, *27*, 4961.

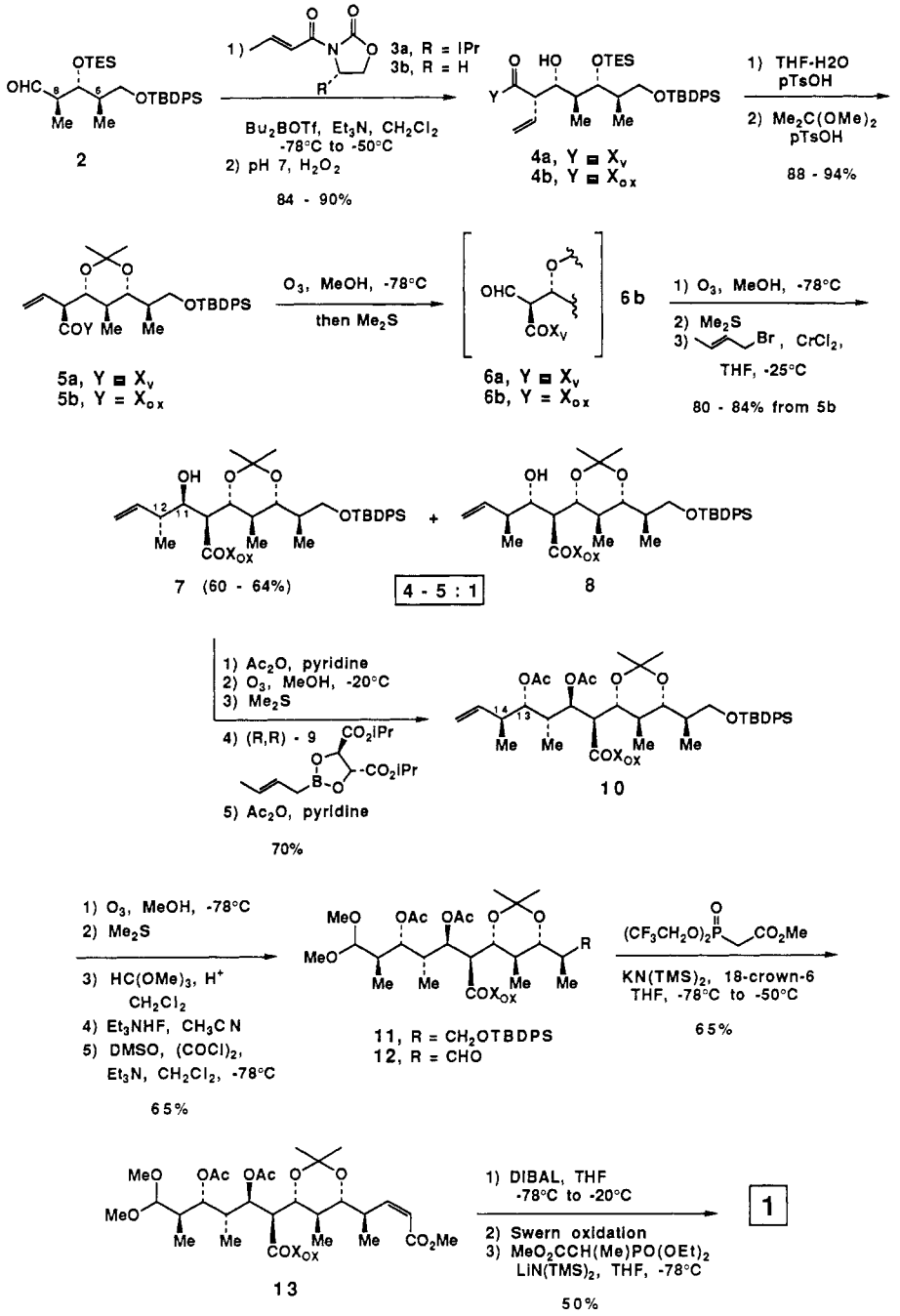
(8) Review of double asymmetric synthesis: Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1.

(9) Additional evidence supporting the stereochemical assignments for **5a,b** was provided by the X-ray structure determination of i that was synthesized from **5a** (via **6a** and **8a**). Details of this synthesis and X-ray analysis will be provided in our full paper. We thank Dr. John C. Huffman for performing the X-ray analysis.



0022-3263/89/1954-3009$01.50/0

Scheme I



procedure discovered thus far for the synthesis of **7** involves treatment of **6b** with the crotylchromium reagent[10] generated from (*E*)-crotyl bromide and $CrCl_2$ (generated in situ by the $LiAlH_4$ reduction of $CrCl_3$) in THF at −25 °C. This provided a 4–5:1 mixture of **7** and **8** in 75–84% yield; the yield of **7** purified chromatographically is 60–64%.[11] The anti relationship between C(11) and C(12) of **7** was verified by selective hydrolysis of the acyloxazolidone (LiOH, H_2O_2, MeOH)[12] followed by treatment of the resulting carboxylic acid with I_2 and $NaHCO_3$ in CH_2Cl_2 that provided iodo lactone **14** in 50% yield.

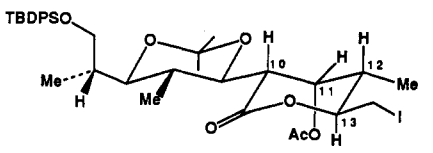
Acylation of **7** followed by ozonolysis, crotylboration with (*R,R*)-tartrate (*E*)-crotylboronate **9**[13] (only one diastereomer was detected), and acylation of the resulting product provided **10** in 70% overall yield. The anti stereochemistry at C(13) and C(14) was verified following conversion to the bisacetonide **15** ((i) TMS-Cl, Et_3N; (ii) O_3, MeOH, −78 °C, then Me_2S; (iii) $NaBH_4$, MeOH; (iv) Et_3NHF, CH_3CN; (v) 2,2-dimethoxypropane, PPTS), the 300-MHz ^1H NMR spectrum (C_6D_6) of which showed $J_{11,12}$ = 8.6 Hz, $J_{12,13}$ = 1.0 Hz, and $J_{13,14}$ = 10.7 Hz. While these data are also consistent with the 12,13-syn stereochemistry in **10**/**15**, this relationship was assigned rigorously by conversion of **10** to **16** ((i) $LiAlH_4$, THF; (ii) 2,2-dimethoxypropane, pTsOH,

(10) (a) Okude, Y.; Hirano, S.; Hiyama, T.; Nozaki, H. *J. Am. Chem. Soc.* **1977**, *99*, 3179. (b) Buse, C. T.; Heathcock, C. H. *Tetrahedron Lett.* **1978**, *19*, 1685.

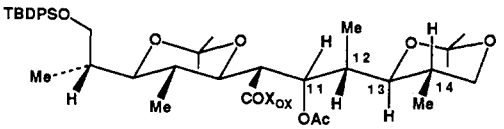
(11) Crotylmetalations of **6a** were much less selective. For example, the reaction of **6a** with the crotylchromium reagent provided a 1:1 mixture of **7a** and **8a** (X_v series), while use of the (*S,S*)-tartrate (*E*)-crotylboronate generated a 15:85 mixture of **7a** and **8a**, respectively. Detailed discussion of these results is deferred to our full paper.

(12) Evans, D. A.; Britton, T. C.; Ellman, J. A. *Tetrahedron Lett.* **1987**, *28*, 6141.

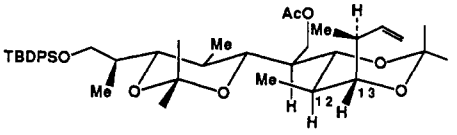
(13) (a) Roush, W. R.; Ando, K. A.; Powers, D. B.; Halterman, R. L.; Palkowitz, A. D. *Tetrahedron Lett.* **1988**, *29*, 5579. (b) Roush, W. R.; Palkowitz, A. D.; Palmer, M. A. J. *J. Org. Chem.* **1987**, *52*, 316.



14 $J_{10,11}$ = 2.8 Hz
$J_{11,12}$ = 1.1 Hz
$J_{12,13}$ = 9.8 Hz



15 $J_{11,12}$ = 8.6 Hz
$J_{12,13}$ = 1.0 Hz
$J_{13,14}$ = 10.7 Hz



16 $J_{11,12}$ = 10.2 Hz
$J_{12,13}$ = 4.0 Hz

CH_2Cl_2; (iii) Ac_2O, pyridine). The 500-MHz ^1H NMR spectrum (C_6D_6) of **16** showed that $J_{11,12}$ = 10.2 Hz, and $J_{12,13}$ = 4.0 Hz.

With the stereochemically complex C(6)–C(14) segment **10** firmly in hand, we turned to the problem of introducing the (2*E*,4*Z*)-dienoate unit of **1**. This necessitated that the vinyl appendage at C(15) first be masked. Thus, ozonolysis of **10** followed by treatment of the intermediate β-acetoxy aldehyde with $HC(OMe)_3$ and PPTS in CH_2Cl_2 provided **11** in 81% yield. The C(5)–TBDPS ether was then cleaved (Et_3NHF, CH_3CN),[14] and the resulting alcohol oxidized by using a standard Swern protocol.[15] Aldehyde **12** (80% from **11**) was then converted to (*Z*)-enoate **13** (65%) by using Still's modification of the Horner–Wadsworth–Emmons (HWE) reaction (>10:1 *Z*:*E*).[16] Selective reduction of the terminal CO_2Me group was accomplished by using a slight excess of DIBAL in THF (−78 °C to −20 °C). The allylic alcohol (70–75% yield) so produced was then oxidized to the (*Z*)-enal, which was subjected to a standard HWE reaction that provided **1** in 50% overall yield from **13**.

In summary, a highly stereoselective synthesis of **1** corresponding to the C(1)–C(15) segment of streptovaricin D has been accomplished. Future reports will describe our efforts to complete a total synthesis of this complex natural product.

Acknowledgment. This research was supported by a grant from the National Institutes of Health (GM 36436).

Supplementary Material Available: Spectroscopic data and physical constants for synthetic intermediates (13 pages). Ordering information is given on any current masthead page.

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