Tetrahedron Letters,Vol.23,No.41,pp 4199-4202,1982 0040-4039/82/414199-04$03.00/0
Printed in Great Britain

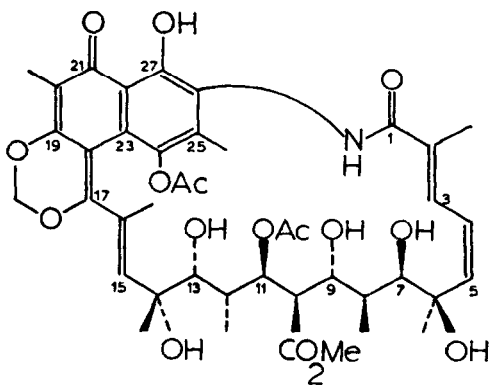
SYNTHESIS OF A KEY INTERMEDIATE FOR THE TOTAL SYNTHESIS OF STREPTOVARICIN A

Peter A. McCarthy

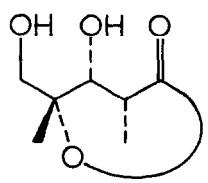
Department of Chemistry, Massachusetts Institute of Technology
Cambridge, Massachusetts 02139

Abstract: A key intermediate (3) for the total synthesis of streptovaricin A (1) is synthesized in its optically active form. Further elaboration of 3 is also described.

Streptovaricin A (1), produced by Streptomyces spectabilis, is an ansamycin antibiotic with notable antitumor activity.[1] The streptovaricins were first isolated by Siminoff and co-workers in 1957[2] and the structures were elucidated by Rinehart and co-workers in the early seventies.[3] The ansa chain [C(1)-C(16)] (2) of streptovaricin A exhibits intriguing structural features. While the chain is rich in chirality with nine asymmetric centers, the presence of hidden symmetry can be easily recognized. Thus, the C(5)-C(9) unit is repeated in the C(15)-C(11) unit and the utilization of this symmetry will simplify the synthetic scheme leading to 2. Herein is described a highly enantioselective synthesis of a key intermediate (3), which is equivalent to the aforementioned C(5)-C(19) unit and will be used twice in the synthesis of the antibiotic.

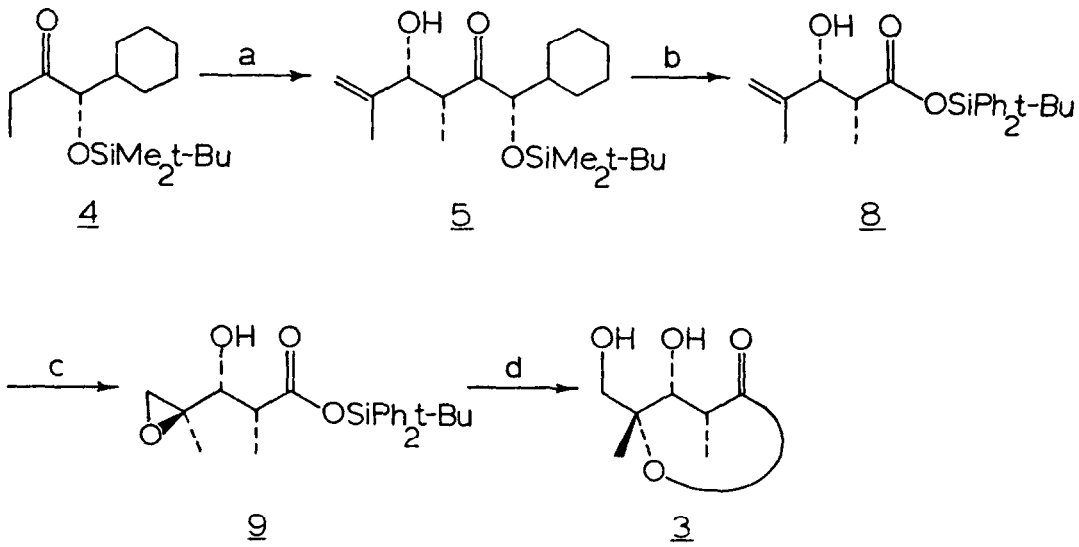


1



3

Scheme 1



4 5 8 9 3

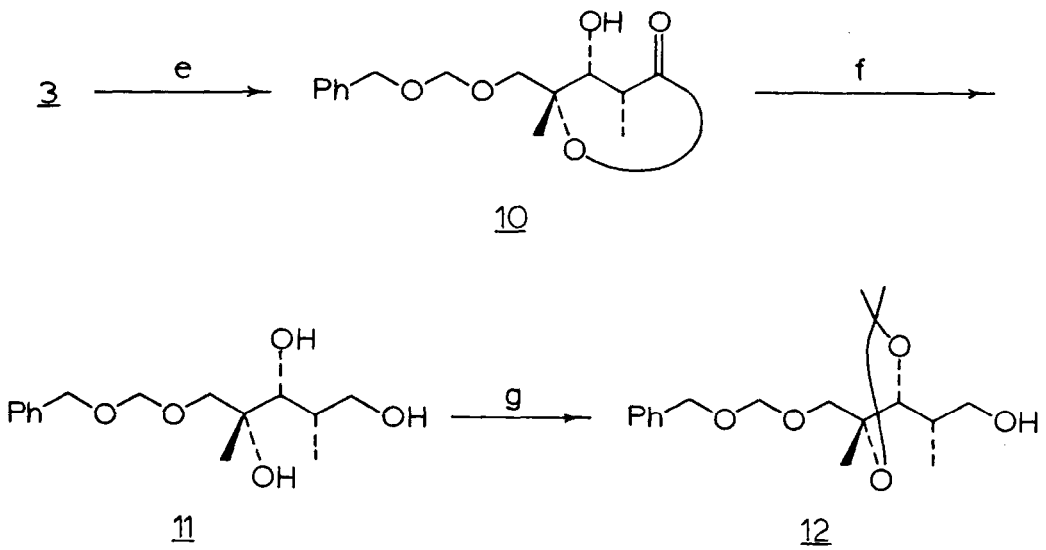
(a) n-Bu_2BOTf, $(i\text{-}Pr)_2NEt$, CH_2Cl_2, 0°C, 6 h; methacrolein, 0°C, 18 h. (b) 1% HF, CH_3CN, RT, 2.5 h; $NaIO_4$ CH_3OH/H_2O, RT, 2 h; t-$BuPh_2SiCl$, imidazole, THF, RT, 12 h. (c) $VO(OEt)_3$, t-BuOOH, NaOAc, CH_2Cl_2, 0°C, 18 h. (d) 1% HF, CH_3CN, RT, 15 min.

The utility of the stereoselective aldol reaction[4,5] has been amply demonstrated in the total synthesis of complex macrolide and ansamycin antibiotics.[6,7] Thus, the chiral boron enolate is generated by treating S-1-cyclohexyl-1-t-butyldimethylsilyloxybutane-2-one (4) with di-n-butylborinyl trifluoromethanesulfonate and diisopropylethylamine in methylene chloride for 6 h at 0°C. Reaction of the enolate with methacrolein proceeded smoothly to provide the aldol adduct (5), mp 33-35°C, in 85% yield with 28:1 stereoselection.[8]

The next transformation involves a stereoselective epoxidation[9] on the terminal double bond of 5. All attempts toward this goal proved unsuccessful, therefore 5 was converted to ester 8 in three steps. Treatment of 5 with 1% HF in MeCN gave the desilylated product 6, which was in turn oxidatively cleaved with sodium meta-periodate. The resulting acid 7 was silylated with t-butyldiphenylsilyl chloride and imidazole to afford ester 8 in 78-85% yield based on 5.

Treatment of 8 with t-butylhydroperoxide in the presence of vanadium triethoxyoxide and sodium acetate led to one epoxide product (9) in 80% yield as expected. The stereochemistry shown in 9 has been assigned to this epoxide based on spectral data and literature precedent.[9] Treatment of 9 with 1% HF in MeCN gave 3, mp 106-106.5°C, in quantitative yield.

Scheme 2



(e) $PhCH_2OCH_2Cl$, $(i\text{-}Pr)_2NEt$, THF, 24 h. (f) LAH, THF, RT, 18 h. (g) acetone, CSA, RT, 20 h.

The key intermediate 3 has been elaborated further as outlined in scheme 2. Selective protection of the primary alcohol with benzyloxymethyl chloride and diisopropylethylamine provided in 98% yield 10 which was in turn reduced with lithium aluminum hydride in THF to give 11 in 92% yield. The 1,3,4-triol 11 was treated with dry acetone and camphorsulfonic acid to yield the 3,4-acetonide 12 in 93% yield with 14:1 selectivity for 12 over the 1,3-acetonide.[10,11]

The above work completes the construction of six chiral centers out of the nine centers present in 2 and work is in progress toward the synthesis of the antibiotic.[12]

Acknowledgments: The author is a John A. Lyons Fellow (1981-83) and gratefully acknowledges partial financial support from the National Institutes of Health (CA 28337). Sincere gratitude is extended to Professors S. Masamune and K.B. Sharpless for helpful discussions. High resolution mass spectra were provided by the facility supported by NIH (Grant RR 00317).

References and Notes

1. Rinehart, Jr., K.L.; Antosz, F.J.; Sasaki, K.; Martin, P.K.; Maheshwari, M.L.; Reusser, F.; Li, L.H.; Moran, D.; Wiley, P.F. Biochem. 1974, 13, 861.
2. Siminoff, P.; Smith, R.M.; Sokolski, W.T.; Savage, G.M. Am. Rev. Tuberc. Pulm. Dis. 1957, 75, 576.
3. For the chemistry of the ansamycins including streptovaricins, see: (a) Brufani, M. in "Topics in Antibiotic Chemistry," Vol. 1, Ed. Sammes, P.; Ellis Horwood Ltd. Sussex, 1977, Part B. (b) Rinehart, Jr., K.L.; Shield, L.S. in "Progress in the Chemistry of Organic Natural Products," Vol. 33, Ed. Herz, W.; Grisebach, H.; Kirby, G.W.; Springer-Verlag, New York, 1976, pp. 231-307.

4. Masamune, S.; Choy, W.; Kerdesky, F.A.J.; Imperiali, B. J. Am. Chem. Soc. 1981, 103, 1566.
5. For other approaches to the stereoselective aldol reaction, see: (a) Evans, D.A.; Nelson, J.V.; Vogel, E.; Taber, T.R. J. Am. Chem. Soc. 1981, 103, 3099. (b) Heathcock, C.H.; Buse, C.T.; Kleschick, W.A.; Pirrung, M.C.; Sohn, J.E.; Lampe, J. J. Org. Chem. 1980, 45, 1066.
6. For a recent review of the chemistry and biochemistry of macrolide antibiotics, see: Masamune, S.; Bates, G.S.; Corcoran, J.W. Angew. Chem. Int. Ed. Engl. 1977, 16, 585.
7. For recent syntheses of macrolides and ansamycins using the aldol approach, see (a) 6-deoxyerythronolide B: Masamune, S.; Hirama, M.; Mori, S.; Ali, Sk. A.; Garvey, D.S. J. Am. Chem. Soc. 1981, 103, 1568. (b) Narbonolide: Kaiho, T.; Masamune, S.; Toyoda, T. J. Org. Chem. 1982, 47, 1612. (c) Tylonolide: (i) Masamune, S.; Kaiho, T.; Garvey, D.S. J. Am. Chem. Soc. submitted for publication. (ii) Masamune, S.; Lu, L.D.-L.; Jackson, W.P. J. Am. Chem. Soc. submitted for publication. (d) Rifamycin S: Masamune, S.; Imperiali, B.; Garvey, D.S. J. Am. Chem. Soc. submitted for publication.
8. The minor isomer was the other 2,3-syn product. No 2,3-anti product was observed. (For definition of syn and anti, see ref. 7c, (i) above). Ratios in this paper based either on high field FTNMR or capillary GC.
9. (a) Rossiter, B.E.; Verhoeven, T.R.; Sharpless, K.B. Tetrahedron Lett. 1979, 4733. (b) Sharpless, K.B.; Verhoeven, T.R. Aldrichimica Acta 1979, 12, 63. Also see (c) Chamberlin, A.R.; Dezube, M.; Dussault, P. Tetrahedron Lett. 1981, 22, 4611.
10. Hayashi, H.; Nakanishi, K.; Brandon, C.; Marmwi, J. J. Am. Chem. Soc. 1973, 95, 8749.
11. The selectivity for five-membered acetonides over six-membered acetonides in triol systems appears to be highly dependent on the character of the alcohols involved (i.e. primary, secondary or tertiary). The 14:1 selectivity noted here for a 1,3,4-triol system is sharply contrasted by the near lack of selectivity observed for a 1,2,4-triol system where alcohol 1 is primary and alcohol 4 is secondary. (Cheng, C.Y.; Masamune, S., unpublished results.)
12. The specific rotations $[\alpha]_D$ (C, concentration) in chloroform of compounds in this work are 3 (26, 0.91) +26.8; 5 (26, 1.12) -14.4; 6 (28, 2.22) +86.5; 7 (27, 0.56) +28.5; 8 (26, 1.23) +22.4; 9 (25, 2.44) +4.7; 10 (26, 0.52) +20.4; 11 (26, 1.70) +24.0; 12 (26, 1.82) -4.0. 250 or 270 MHz proton FTNMR data for new compounds (in $CDCl_3$). 3 δ 3.92 (d, J=12.18, 1H), 3.91 (dd, J=2.02, 8.88, 1H), 3.81 (d, J=12.18, 1H), 3.10 (broad, 1H), 2.89 (dq, J=7.33, 8.88, 1H), 1.92 (d, J=2.02, 1H), 1.39 (s, 3H), 1.33 (d, J=7.33, 3H); 5 δ 5.15 (s, 1H), 4.96 (q, J=0.90, 1H), 4.32 (dd, J=2.03, 2.05, 1H), 3.89 (d, J=5.87, 1H), 3.53 (d, J=2.03, 1H), 3.11 (dq, J=2.05, 7.30, 1H), 1.77-1.05 (m, 11H), 1.68 (s, broad, 3H), 1.02 (d, J=7.3, 3H), 0.94 (s, 9H), 0.05 (s, 3H), 0.02 (s, 3H); 6 (+D_2O) δ 5.09 (s, 1H), 4.95 (d, J=1.22, 1H), 4.38 (d, J=3.11, 1H), 4.18 (d, J=2.45, 1H), 2.93 (dq, J=3.11, 7.26, 1H), 1.82-1.14 (m, 11H), 1.68 (s, broad, 3H), 1.09 (d, J=7.26, 3H); 7 δ 5.07 (s, 1H), 4.95 (s, 1H), 4.45 (d, J=3.90, 1H), 2.72 (dq, J=3.90, 7.10, 1H), 1.71 (s, 3H), 1.13 (d, J=7.10, 3H); 8 δ 7.74-7.67 (m, 4H), 7.48-7.36 (m, 6H), 5.12 (s, 1H), 4.96 (q, J=1.71, 1H), 4.53 (m, 1H), 2.84 (dq, J=3.91, 6.84, 1H), 2.51 (d, J=3.91, 1H), 1.74 (s, broad, 3H), 1.23 (d, J=6.84, 3H), 1.13 (s, 9H); 9 (+D_2O) δ 7.73-7.69 (m, 4H), 7.48-7.34 (m, 6H), 4.40 (d, J=3.20, 1H), 3.05 (d, J=4.79, 1H), 2.83 (dq, J=3.20, 7.14, 1H), 2.66 (d, J=4.79, 1H), 1.38 (s, 3H), 1.23 (d, J=7.14, 3H), 1.13 (s, 9H); 10 δ 7.38-7.30 (m, 5H), 4.78 (d, J=15.16, 1H), 4.75 (d, 15.16, 1H), 4.62 (d, J=11.78, 1H), 4.56 (d, J=11.78, 1H), 3.89 (d, J=10.94, 1H), 3.84 (dd, J=9.28, 9.98, 1H), 3.75 (d, J=10.94, 1H), 2.85 (dq, J=7.31, 9.28, 1H), 2.56 (d, J=9.98, 1H), 1.40 (s, 3H), 1.32 (d, J=7.31, 3H); 11 (+D_2O) δ 7.36-7.29 (m, 5H), 4.78 (s, 2H), 4.61 (s, 2H), 3.78 (d, J=2.15, 1H), 3.66 (dd, J=4.04, 10.53, 1H), 3.58 (dd, J=6.28, 10.53, 1H), 3.55 (s, 2H), 1.87 (m, 1H), 1.18 (s, 3H), 1.03 (d, J=7.06, 3H); 12 (+D_2O) δ 7.36-7.23 (m, 5H), 4.82 (d, J=8.15, 1H), 4.79 (d, J=8.15, 1H), 4.65 (d, J=12.16, 1H), 4.60 (d, J=12.16, 1H), 3.92 (d, J=8.51, 1H), 3.69 (d, J=10.49, 1H), 3.62 (dd, J=4.43, 11.30, 1H), 3.59 (d, J=10.49, 1H), 3.54 (dd, J=4.59, 11.30, 1H), 1.89 (m, 1H), 1.44 (s, 3H), 1.35 (s, 3H), 1.21 (s, 3H), 1.14 (d, J=6.69, 3H).

(Received in USA 9 June 1982)