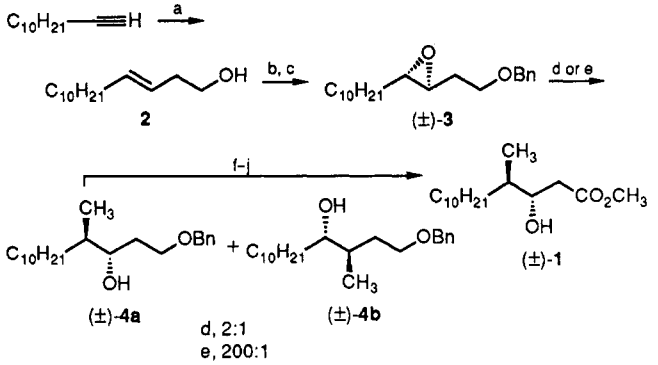
Scheme II[a]



[a] (a) DIBAL; then *n*-BuLi, ethylene oxide (69% yield). (b) NaH, benzyl chloride in DMSO (68% yield). (c) *m*-CPBA (79% yield). (d) $LiMe_2Cu$, ether, 0 °C (60% yield; **4a**:**4b** = 2:1) or (e) 2 equiv of Me_3Al–*n*-BuLi, hexane, 0 °C (80% yield; **4a**:**4b** > 200:1). (f) TBDMSCl, imidazole (91% yield). (g) H_2/Pd–C (97% yield). (h) PDC in DMF. (i) CH_2N_2 (g, h: 62% yield). (j) Tetrabutylammonium fluoride in THF (77% yield).

the crude CDPC 3510 was further purified by methods that have been previously described.[5] Hydrolysis of 1.237 g of CDPC 3510 with 5 M HCl (100 °C; 2 h) and ether extraction of the hydrolysate afforded 0.252 g of a crude hydroxyalkanoic acid. These conditions are considerably milder than a previously described hydrolytic degradation[1] and afforded in the present case a saturated hydroxyalkanoic acid with only slight (<5 mol %) contamination by a dehydration product.[6] The crude product mixture was methylated with excess diazomethane, and 0.247 g of a homogeneous β-hydroxy ether, (−)-**1**, was isolated by column chromatography on silica gel using 19:1 hexane–ether as the eluent (Scheme I).

Although the methylated fatty acid obtained from CDPC 3510 is diastereomerically homogeneous and its ^1H NMR and ^{13}C NMR spectral characteristics[7] are compatible with the gross structure suggested by Carr et al. (vide supra), there is no evidence within our spectroscopic data that would allow us to make a firm assignment of the C(3)–C(4) relative stereochemistry of (−)-**1**.[8]

A syn-selective aldol method[9] provided us with a mixture of racemic methyl 3-hydroxy-4-methyltetradecanoate diastereomers (syn:anti = 1.5:1), however, spectroscopic comparison of the homogeneous natural material with the synthetic mixture indicated that the CDPC 3510 degradation product was identical with our minor synthetic product. Therefore, we abandoned the aldol strategy and turned to an approach that required the stereospecific anti addition of a methyl group to C(4) of racemic *trans*-1-(benzyloxy)-3,4-epoxytetradecane, (±)-**3**, in order to establish the correct C(3)–C(4) stereochemistry in an intermediate to be carried on to (±)-**1**. Compound (±)-**3**, prepared in three steps from 1-dodecyne (Scheme II), was allowed to react with lithium dimethylcuprate (ether, 0 °C) to give a disappointing 2:1 mixture of regioisomers (±)-**4a** and (±)-**4b**, which, however, were easily separated and characterized. On the other hand, treatment of compound (±)-**3** with a reagent formed in hexane from 3 equiv of Me_3Al and 1.5 equiv of *n*-BuLi[10,11] proved to be stereospecific and highly C(4) selective to give the desired product (**4a**:**4b** > 200:1). Compound (±)-**4a** was then carried on in five steps to (±)-**1** (16% overall), which proved identical (^1H and ^{13}C NMR, TLC) with authentic CDPC 3510 β-hydroxy ester.

Acknowledgment. This work was supported in part by a Cottrell grant from Research Corporation and in part by a grant from the donors of the Petroleum Research Fund, administered by the American Chemical Society.

Supplementary Material Available: Detailed conditions for the isolation and hydrolytic degradation of CDPC 3510, a scheme describing the syn-selective aldol preparation of methyl (±)-3-hydroxy-4-methyltetradecanoate, experimental procedures for the steps of Scheme II, and complete spectral and analytical data for compounds (±)-**3** (±)-**4a**, (±)-**4b**, and (±)-**1** (4 pages). Ordering information is given on any current masthead page.

(5) Burmeister, H. R.; Vesonder, R. F.; Peterson, R. E.; Costello, C. E. *Mycopathologia* **1985**, *91*, 53.

(6) More vigorous hydrolysis conditions have been reported to give a β,γ-unsaturated carboxylic acid side product presumed to be 4-methyl-3-decenoic acid (ref 1). The α,β-unsaturated ester isolated after methylation of our CDPC 3510 hydrolysate exhibited the following characteristics: ^1H NMR ($CDCl_3$, 300 MHz) δ 6.98 (dd, *J* = 17, 7 Hz, 1 H), 5.77 (d, *J* = 17 Hz, 1 H), 3.75 (s, 3 H), 2.32 (m, 1 H), 1.35–1.10 (m, 18 H), 1.05 (d, *J* = 7 Hz, 3 H), 0.83 (t, *J* = 7 Hz, 3 H).

(7) (−)-**1**: ^1H NMR ($CDCl_3$, 300 MHz) δ 3.87 (ddd, *J* = 9.4, 5.5, 3.2 Hz, 1 H), 3.71 (s, 3 H), 2.86 (br s, 1 H), 2.49 (dd, *J* = 16.5, 3.2 Hz, 1 H), 2.40 (dd, *J* = 16.5, 9.4 Hz, 1 H), 1.60 (m, 1 H), 1.28–1.22 (m, 18 H), 0.88 (d, *J* = 6.8 Hz, 3 H), 0.87 (t, *J* = 6.8 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 173.9, 71.9, 51.7, 38.2, 37.7, 32.3, 31.9, 29.9, 29.6, 29.3, 27.1, 22.7, 14.9, 14.1; $[\alpha]^{24}_D$ = −8.5° (CH_2Cl_2; *c* = 2.7). Anal. Calcd for $C_{16}H_{32}O_3$: C, 70.54; H, 11.84. Found: C, 70.32; H, 11.80.

(8) The main difficulty in assigning the relative stereochemistry of 3-hydroxy-4-methylalkanoic acid derivatives arises from the fact that C(4) lies outside of the six-member ring defined by hydrogen bonding between the carbonyl group and the C(3) hydroxyl substituent in these compounds thus, the typical H(3)–H(4) coupling constants (*J* = 5.5 Hz in (−)-**1**) cannot be relied on in the absence of authentic standards. For example, $J_{H(3),H(4)}$ = 4.5 Hz in methyl (±)-*syn*-3-hydroxy-4-methylhexanoate (cf. ref 10).

(9) For a related example, see: Heathcock, C. H.; Flippin, L. A. *J. Am. Chem. Soc.* **1983**, *105*, 1667.

(10) Flippin, L. A.; Brown, P. A.; Jalali-Araghi, K. Manuscript submitted to *J. Org. Chem.*

(11) For related examples of previous work in this area, see: (a) Mori, K.; Nakazono, Y. *Tetrahedron* **1986**, *42*, 6459. (b) Herold, P.; Mohr, P.; Tamm, C. *Helv. Chim. Acta* **1983**, *66*, 744. (c) Pfaltz, A.; Mattenberger, A. *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 71.

Oxidative Coupling Reactions of Phenols with $FeCl_3$ in the Solid State

Fumio Toda,* Koichi Tanaka, and Shinji Iwata

Department of Industrial Chemistry, Faculty of Engineering, Ehime University, Matsuyama 790, Japan

Received February 14, 1989

Summary: Some oxidative coupling reactions of phenols with $FeCl_3$ are faster and more efficient in the solid state than in solution. Some coupling reactions in the solid state are accelerated by irradiation with ultrasound. Some coupling reactions are achieved by using a catalytic amount of $FeCl_3$.

Sir: Oxidative couplings of phenols are usually carried out by treatment of phenols in solution with more than equimolar amount of metal salts such as $FeCl_3$ or manganese tris(acetylacetonate), although the latter one is too expensive to use in a large quantity. The coupling reactions of phenols with $FeCl_3$, however, sometimes give

0022-3263/89/1954-3007$01.50/0

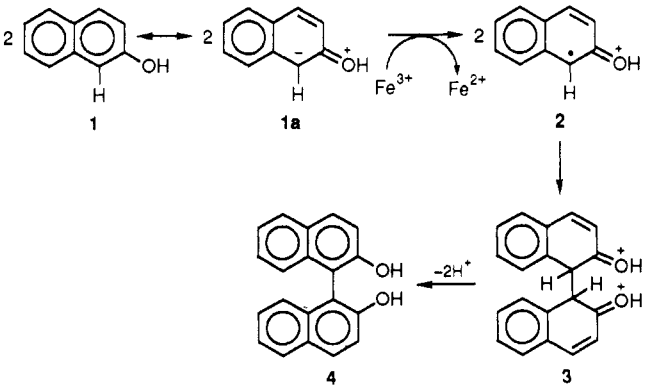
Table I. Oxidative Coupling Reactions in the Solid State

reactant	reaction conditions: state[a]	reagent[b]	temperature, °C	time, h	product	yield, %
1	K	I	50	2	4	95
1	K	I	rt[c]	144	4	93
1	U	I	50	2	4	91
1	U	II	50	5	4	79
5	U	II	50	9	6	68
5	U	II	rt	9	6	0
5	K	II	50	9	6	20
7	K	I	50	1	8	66
7	U	I	50	1	8	89
7	S	I	50	1	8	84
9	U	II	50	1	10	64
11	U	I	rt	6	12	82
11	U	I	50	6	12	97
11	K	I	rt	12	12	0
11	K	I	50	6	12	77
11	S	I	rt	6	12	0

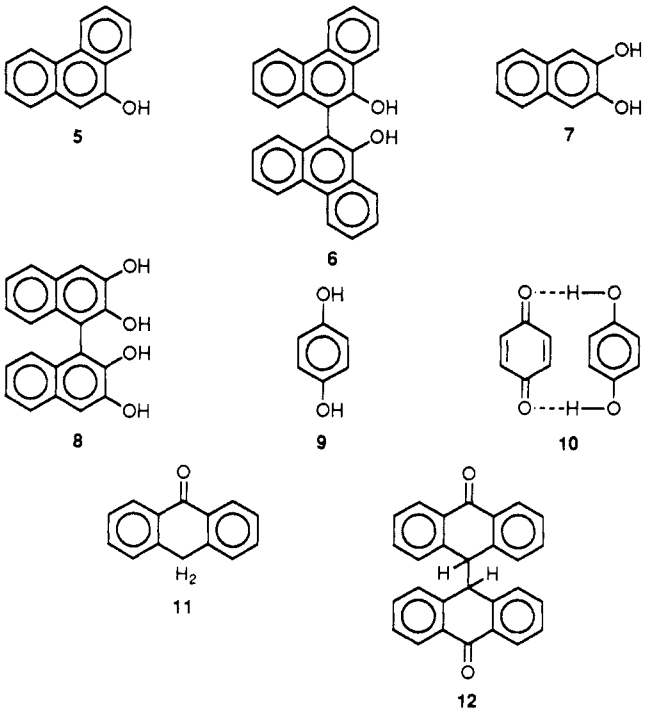
[a] K, keeping; S, shaking; U, ultrasound (28 kHz). [b] I, $FeCl_3 \cdot 6H_2O$; II, $[Fe(DMF)_3Cl_2][FeCl_4]$. [c] Room temperature.

quinones as byproducts. Recently we found that the coupling reaction with $FeCl_3$ proceeds much faster and more efficiently in the solid state than in solution and that the reaction in the solid state is accelerated by irradiation with ultrasound. We also found that the coupling reaction in the solid state can be achieved by using a catalytic amount of $FeCl_3$.

A mixture of 1 (1 g, 7 mmol) and $FeCl_3 \cdot 6H_2O$ (reagent I, 3.8 g, 14 mmol) was finely powdered by agate mortar and pestle. The mixture was then put in a test tube and kept at 50 °C for 2 h. Decomposition of the reaction mixture with dilute HCl gave 4 in 95% yield (Table I). Almost the same result was obtained when finely powdered 1 and I were mixed by shaking in a test tube for 5 min and then treated as above. In both cases, particle size of the materials was 50–100 μm. Contrarily, heating of a solution of 1 (1 g) and I (3.8 g) in 50% aqueous MeOH (10 ml) under reflux for 2 h gave 4 in 60% yield.[1] It is clear that the reaction in the solid state is more efficient than in solution. However, the reaction in the solid state proceeds very slowly at room temperature and is not accelerated by irradiation with ultrasound (Table I). Nevertheless, it is surprising that one electron oxidation of 1 to the radical species 2 with Fe^{3+} and coupling of 2 to 3 occur more easily in the solid state than in solution. Water molecules of I would not be essential for the coupling reaction, because the irradiation with ultrasound to a mixture of finely powdered 1 and $[Fe(DMF)_3Cl_2][FeCl_4]$ (reagent II)[2] at 50 °C in the solid state gave 4 in 79% yield (Table I).



When a mixture of finely powdered 5 and two molar amounts of II was irradiated with ultrasound at 50 °C for 9 h in the solid state, 6 was obtained in 68% yield (Table I). Contrarily, keeping of a solution of 5 and two molar amounts of II in CH_2Cl_2 at room temperature for 48 h gave 6 in 33% yield in addition to byproducts such as 9-phenanthrone and 9,10-phenanthrenequinone. In this case, it is difficult to isolate 6 in pure state. When a mixture of finely powdered 7 and two molar amounts of I was kept at 50 °C for 1 h in the solid state, 8 was obtained in 66% yield (Table I). On the other hand, when the mixture was irradiated with ultrasound and shaken at 50 °C for 1 h, 8 was obtained in 89 and 84% yields, respectively (Table I).



Irradiation with ultrasound to a mixture of finely powdered 9 and two molar amounts of II at 50 °C for 1 h gave 10 in 64% yield (Table I). Not only phenols but also their keto forms gave coupling products by treatment with I in the solid state. Irradiations with ultrasound to a mixture of finely powdered 11 and two molar amounts of II at room temperature and 50 °C gave 12 in 82 and 97% yields, respectively (Table I).

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(2) Tobinaga, S.; Kotani, E. *J. Am. Chem. Soc.* **1972**, *94*, 309.

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.

Acknowledgment. We thank the Ministry of Education, Science and Culture for Grant-in-Aid for Developmental Scientific Research (Grant No. 63840017).

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

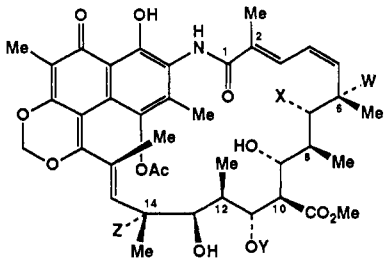
William R. Roush* and Alan D. Palkowitz†

Department of Chemistry, Indiana University, Bloomington, Indiana 47405

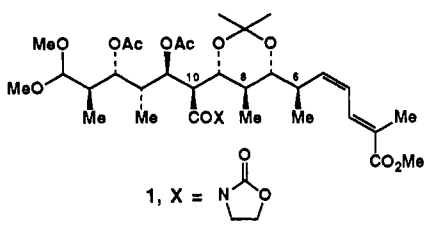
Received April 20, 1989

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.

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(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.

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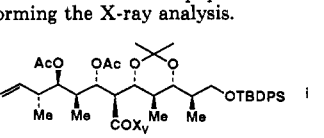
(8) Review of double asymmetric synthesis: Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1.

(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.



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