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A New Approach to the Synthesis of γ-Hydroxy-α,β-unsaturated Macrolides and (-)-Pyrenophorin by Intramolecular C=C Bond Formation with Oxidative Functionalization from ω-[α-(p-Chlorophenylsulfinyl)acetoxy]alkanal

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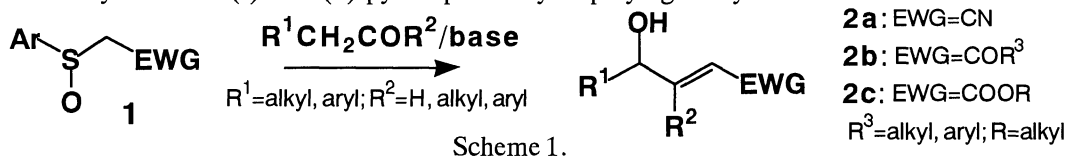
The title compounds were prepared via the intramolecular condensation reaction of 12-[α-(p-chlorophenylsulfinyl)acetoxy]tridecanal(or dodecanal) or via the combination of inter- and intramolecular condensation of 5-[α-(p-chlorophenylsulfinyl)acetoxy]hexanal in the presence of piperidine.

In the macrolide synthesis, we have two attractive points; how to cyclize acyclic compounds into macrolides and how to build and protect required functionalities in the synthesis of acyclic compounds. Much attention has been focused on the cyclization by intramolecular esterification of suitable hydroxy carboxylic acids[1] and by intramolecular C-C bond formation, such as alkylation,[2] aldol-type reaction,[3] 1,3-dipolar cycloaddition,[4] and Wittig-type reaction.[5]

We have been taking great interest in the synthesis of bioactive compounds by using organosulfur compounds, because a sulfur functional group plays remarkable roles not only in C-C bond formation but also in desulfurizative functionalization of the C-C bond formed. For example, we[6a,b] and Tanikaga et al.[6c] reported the reaction of sulfinyl-activated methylene compound (**1**) with aldehydes (or ketones) to give γ-hydroxy-α,β-unsaturated nitriles (**2a**),[6a] ketones (**2b**),[6b] esters (**2c**),[6c] under mild reaction conditions (Scheme 1). The reaction seems to be advantageous for the synthesis of biologically attractive macrolides such as pyrenophorin (**3**),[7a] brefeldin A,[7b] aspicilin,[7c] and A26771B[7d] which have γ-hydroxy(or γ-oxo)-α,β-unsaturated lactone functionalities. Actually, we and Corey et al.[8] have succeeded in the synthesis of (+)-brefeldin A using the reaction to build γ-hydroxy-α,β-unsaturated ester functionality. Here, we wish to propose a new and facile approach to the synthesis of (-)- and (+)-pyrenophorin by employing the cyclization reaction to macrolides.



Scheme 1.

First, we tried the intramolecular reaction of the aldehydes having a sulfinyl-activated methylene functionality, 12-[α-(p-chlorophenylsulfinyl)acetoxy]dodecanal **4a**, 12-[α-(p-chlorophenylsulfinyl)acetoxy]-tridecanal **4b**, 10-[α-(p-chlorophenylsulfinyl)acetoxy]decanal **4c**, and 10-[α-(p-chlorophenylsulfinyl)acetoxy]-undecanal **4d**, and found out that *E* geometrical 15-membered γ-hydroxy-α,β-unsatulated lactones (**5a** and **5b**) were successfully obtained under high dilution conditions, though the yields of 13-membered ring products **5c-d** were low (Table 1).

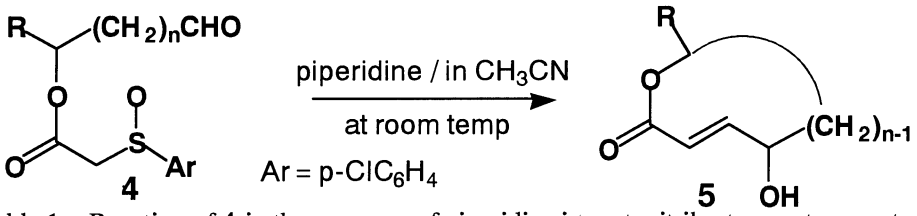


Table 1. Reaction of **4** in the presence of piperidine in acetonitrile at room temperature

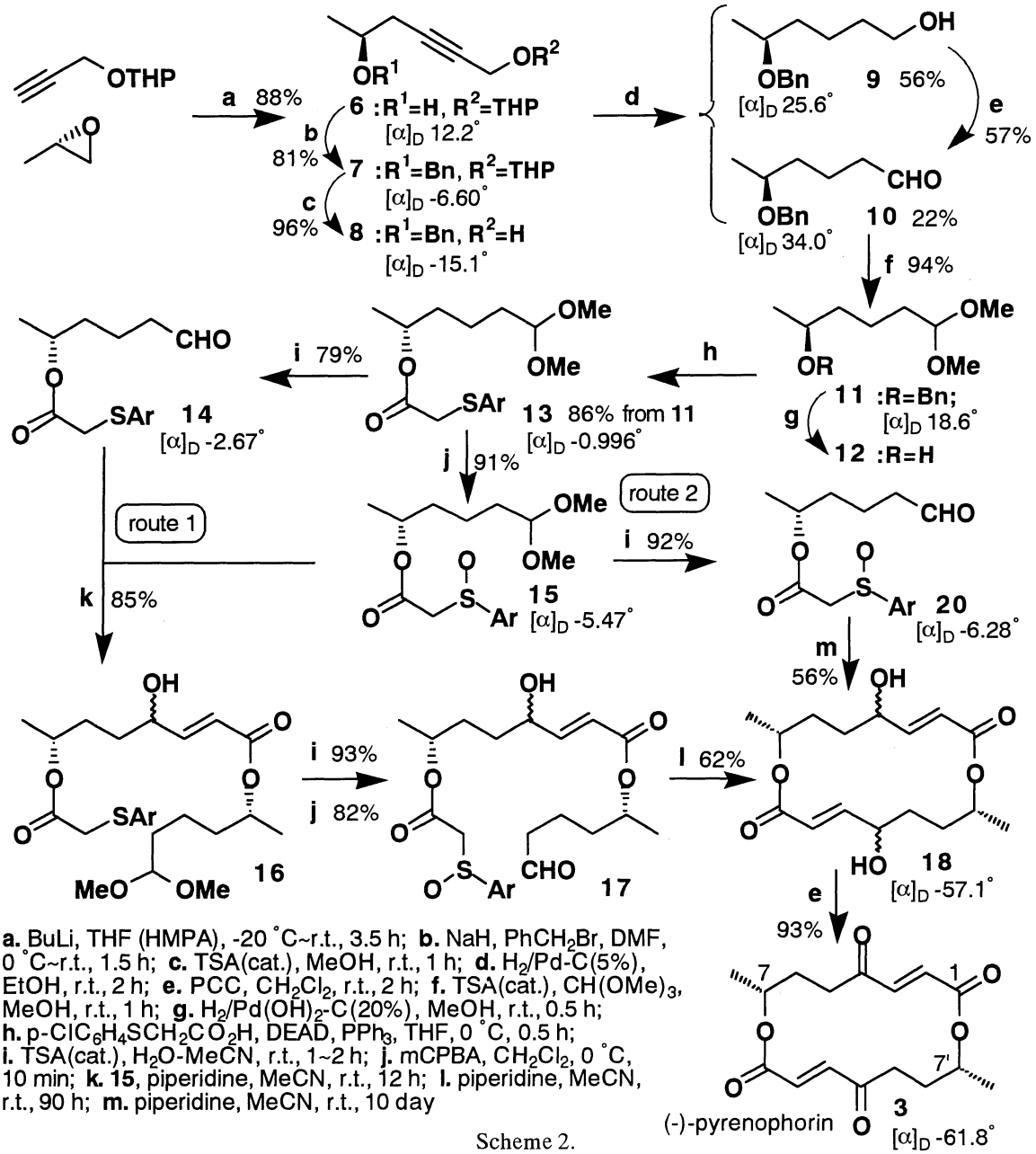
4	R=	n=	Substrate mmol/l	Piperidine mmol/l	Reaction time/day	5	yield/%
4a	H	10	0.53	24	3	**5a**	81
4b	Me	10	1.2	1.4	2	**5b**	40
4b	Me	10	1.2	2.2	2.5	**5b**	45
4b	Me	10	0.53	24	3	**5b**	61
4c	H	8	0.53	24	4	**5c**	30
4d	Me	8	0.53	24	6	**5d**	<20

Next, on the basis of this finding, we tried to synthesize the widely known macrolide pyrenophorin (**3**) having a 16-membered C_2-symmetrical dilactone structure. In its synthesis, the attractive point is cyclization of the monomeric or dimeric acyclic molecule to the dilactone. The most popular method is lactonization by the Mitsunobu reaction[1j-r] of the corresponding hydroxy carboxylic acid, in which preliminary formation and/or protection of α,β-unsatulated and γ-oxo functionalities are required. Recently, the ring-closure via the intramolecular Wittig-type olefination[5] (the Wadsworth-Emmons olefination) was effectively used by Takano et al.,[5c] in which they succeeded in the preparation of the aldehydephosphonoacetate having masked carbonyl (latent γ-oxo) funtionality. On the other hand, our method seems more convenient, because it is not necessary to form the γ-hydroxy-α,β-unsaturated functionality on the aldehyde chain before the ring-closure as shown above.

For our (-)- and (+)-pyrenophorin synthesis, (*S*)-propylene oxide[9] was used to build the C-7 and 7' chiralities. The propylene oxide was treated with lithium 3-tetrahydropyranyloxypropynylide, derived from 3-tetrahydropyranyloxypropyne and n-BuLi, to give the optically active alcohol **6**. The hydroxy group of **6** was converted to the benzyl ether (**7**), and then the THP-ether of **7** was hydrolyzed to (*S*)-5-benzyloxyhex-2-yn-1-ol (**8**). Hydrogenation of **8** gave a mixture of 5-benzyloxyhexanol (**9**) and 5-benzyloxyhexanal (**10**) (ca. 2:1). The alcohol **9** was converted to the aldehyde **10** by pyridinium chlorochromate(PCC)-oxidation. The dimethylacetal **11** was prepared to protect the carbonyl of the benzyloxy aldehyde **10** by treatment with methyl orthoformate and catalytic amounts of p-toluenesulfonic acid (TSA), and the benzyl-protection was removed by $Pd(OH)_2$-catalized hydrogenation to give hydroxy dimethylacetal **12**. Treatment of the alcohol **12** with α-(p-chlorophenylthio)acetic acid under the Mitsunobu-conditions[10] gave (*R*)-5-(α-p-chlorophenylthio)acetoxy-1,1-dimethoxyhexane **13**. Our cyclization was achieved by the following two routes using **13** as a key intermediate.

The sulfide **13** was hydrolyzed to the aldehyde **14** and treated with the sulfoxide **15**, derived by the mCPBA-oxidation of **13**, in the presence of piperidine to give the *E* geometrical dimer **16**. The sulfide **16** was converted into the pyrenophorol precursor, sulfinyl-activated methylene aldehyde **17**, via the acid-hydrolysis of the dimethylacetal into aldehyde followed by the oxidation of the sulfide into sulfoxide. Treatment of highly diluted **17** in acetonitrile with piperidine gave the all *E* geometrical diastereomixture of pyrenophorol (**18**) in 62% yield and the *E* and *Z* mixed-product **19** (19%). Similar treatment of **20**, derived by acid-hydrolysis of **15**, also gave **18** in 56% yield together with eight membered ring product (17%) and **19** (trace). (-)-Pyrenophorin (**3**) was obtained by PCC-oxidation of diastereomixture of **18** in 93% yield. Moreover, (+)-**3** ($[\alpha]_D$ 65.4°) was also

obtained by the same procedure from (*S*)-5-(α-p-chlorophenylthio)acetoxy-1,1-dimethoxyhexane (+)-**13** ([α]$_D$1.27°) derived by treatment of **12** with α-(p-chlorophenylthio)acetyl chloride and triethylamine.



a. BuLi, THF (HMPA), -20 °C~r.t., 3.5 h; **b.** NaH, $PhCH_2Br$, DMF, 0 °C~r.t., 1.5 h; **c.** TSA(cat.), MeOH, r.t., 1 h; **d.** H_2/Pd-C(5%), EtOH, r.t., 2 h; **e.** PCC, CH_2Cl_2, r.t., 2 h; **f.** TSA(cat.), $CH(OMe)_3$, MeOH, r.t., 1 h; **g.** H_2/$Pd(OH)_2$-C(20%), MeOH, r.t., 0.5 h; **h.** p-$ClC_6H_4SCH_2CO_2H$, DEAD, PPh_3, THF, 0 °C, 0.5 h; **i.** TSA(cat.), H_2O-MeCN, r.t., 1~2 h; **j.** mCPBA, CH_2Cl_2, 0 °C, 10 min; **k. 15**, piperidine, MeCN, r.t., 12 h; **l.** piperidine, MeCN, r.t., 90 h; **m.** piperidine, MeCN, r.t., 10 day

Scheme 2.

This is the first example of the macrolide synthesis by intramolecular reaction of the aldehyde having a sulfinyl-activated methylene functionality, in which the sulfur functional group plays notable roles; acceleration of the C=C bond formation and oxidation of the γ-carbon atom with desulfurization.

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