NEW ENTRY TO DIASTEREOSELECTIVE SYNTHESIS OF β,γ-DISUBSTITUTED γ-LACTONES. APPLICATION TO "SELF-IMMOLATIVE" ENANTIOSELECTIVE SYNTHESIS OF 5-ALKYLBUTENOLIDES

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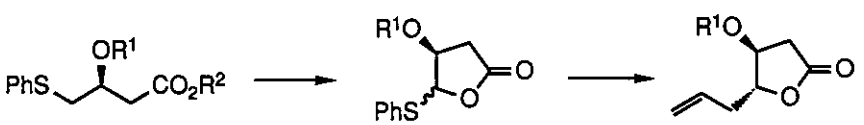
Abstract—Photo-initiated radical allylation of γ-phenylthio-γ-lactones (**5a,b** and **6b**), derived from 3-hydroxy-4-(phenylthio)butyrates, gave *trans* β-oxygenated γ-allyl-γ-lactones (**7a,b**) in high degree of diastereoselectivity. The method was applied to enantioselective synthesis of (*R*)-5-(2-hydroxyethyl)-2,5-dihydro-2-furanone (**11**) with high optical purity.

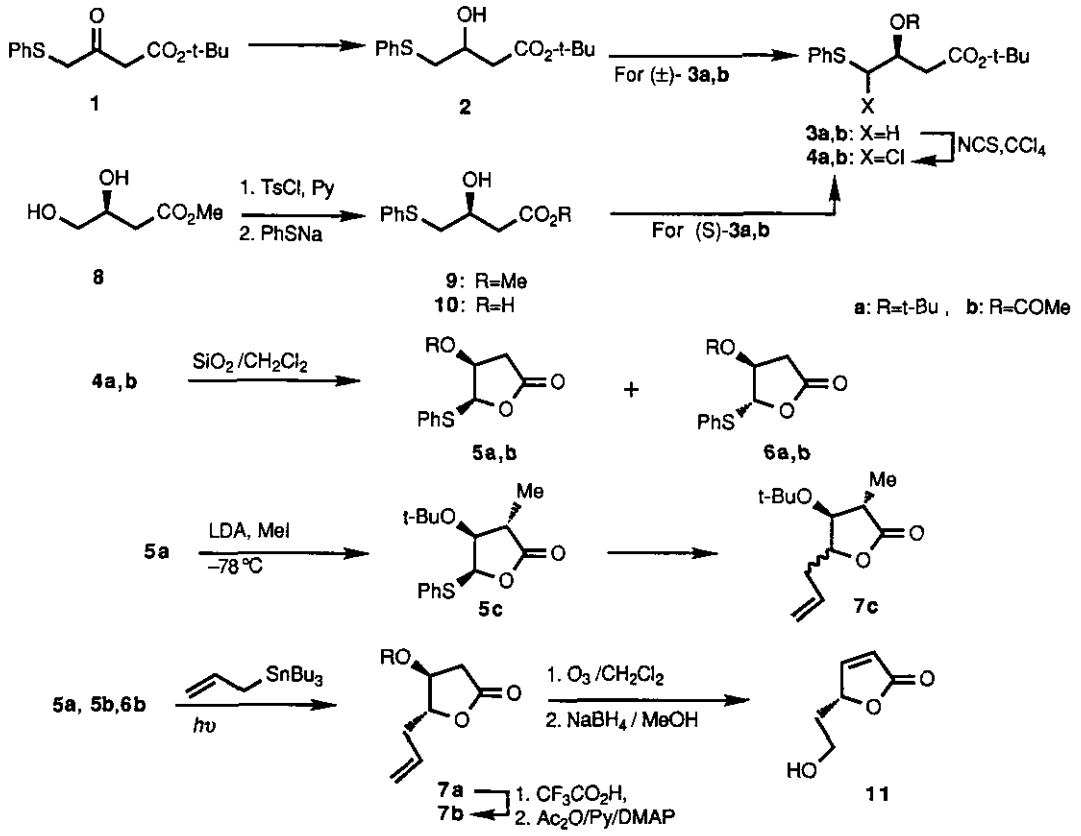
Recently we have reported a new method for stereocontrolled synthesis of 2-amino alcohols, based on sulfonium ion induced cyclocarbamation of *N*-(β-phenylthio)carbamates and subsequent radical allylation reactions.[1] This method was applied to a diastereocontrolled construction of vicinal stereogenic centers on five membered heterocycles such as 4,5-disubstituted oxazolidin-2-ones. In this paper we disclose the extention of the strategy to a diastereoselective synthesis of β-oxygenated γ-allyl-γ-lactones as outlined in Eq. 1 and the application to "self-immolative" synthesis[2] of 5-alkylbutenolide with high enantioselectivity.



Eq. 1

At first, a series of racemic 3-oxygenated 4-(phenylthio)butyrates were prepared as follows to examine the feasibility and efficiency of the process delineated in Eq. 1. 4-Phenylthio-3-oxobutanoate (**1**), prepared from *t*-butyl acetoacetate through dianion method (NaH, *n*-BuLi, PhSSPh), was reduced with $NaBH_4$ in EtOH to give *t*-butyl hydroxyester (**2**) in 95% yield.[3]

Treatment of **2** with excess isobutene in the presence of *p*-TsOH in CH_2Cl_2 gave *t*-butyl *t*-butoxyester (**3a**) in 45% yield together with 30% of recovered **2**. Acetylation of **2** (Ac_2O, Py) gave **3b** in 95% yield.



Reaction of **3a,b** with *N*-chlorosuccinimide (CCl_4, room temperature, 1 h) yielded the corresponding α-chloro sulfides (**4a,b**), which were submitted to cyclization reaction without purification. Lactonization of **4a,b** was best conducted under the influence of silica gel in CH_2Cl_2 at room temperature to give *cis*-phenylthiolactones (**5a,b**)[4] and *trans*-isomers (**6a,b**),[4] respectively (**5a**/**6a**=5; 72%, **5b**/**6b**=1; 88%).[5] These were readily separated by column chromatography on silica gel. The stereostructures of **5a** and **6a** were deduced from their ^{1}H-nmr spectra. The signals due to C(5)-H of **5a** appeared at δ 5.83 as a doublet (J=5.2 Hz), but that of **6a** resonated at δ 5.56 as a doublet (J=2.9 Hz). The stereochemistry of **5a** was unambiguously confirmed to be cis by NOE experiment on **5a** and **6a**. Large NOE enhancement (8-11%) between C(4)-H and C(5)-H was

observed for **5a**, while relatively small NOE (1-3%) for **6a** was measured. Photo-initiated radical allylation reaction of **5a** according to the conditions reported previously[1] [(n-$Bu_3Sn)_2$ (1 equiv.), n-$Bu_3SnCH_2CH{=}CH_2$ (4 equiv.) in toluene-MeCN (0.5 M solution), 500 W Hg-lamp, 30 h] gave allylation product (**7a**)[6] as a single isomer in 50% yield. α-Oriented methyl subustituent of **5c**, prepared stereoselectively through methylation (LDA, MeI, –78 °C) of **5a**, influenced the stereochemical course of the reaction and no diastereoselectivity (*cis*/*trans* 1:1) was observed in a formation of **7c**. Allylation of **5b** and **6b** under the same conditions as above afforded **7b**[6] in virtually the same yields (55% from **5b**, 58% from **6b**)[1,7] without a detectable amount of stereoisomer. Thus a mixture of **5b** and **6b** was used, without separation, for a synthesis of **7b** practically.

Next, our attention was turned to the enantioselective synthesis of 5-alkylbutenolides in "self-immolative" manner as an application of this methodology, which was also useful to confirm the stereostructures of **7a,b**. The required optically active isomers of **3a,b** were readily synthesized from (*S*)-malic acid as follows. Mono-tosylation of diol (**8**)[8] followed by treatment with benzenethiolate (PhSH, NaH, THF) gave **9**, oil; $[\alpha]_D$ –6.1° (c 0.8, $CHCl_3$), in 55% yield. After hydrolysis of **9**, the acid (**10**), mp 95-97 °C, was converted to (*S*)-enantiomer of **2**, which was transformed to (+)-**7a**, $[\alpha]_D$ +62.5°(c 0.5, $CHCl_3$), and (–)-**7b**, $[\alpha]_D$ –17.3°(c 1.0, $CHCl_3$), *via* (–)-**5a** and (+)-**5b**, (–)-**6b** by exactly the same procedure as described for racemic series, respectively. Ozonolysis (–78 °C in CH_2Cl_2) of (–)-**7b** followed by reductive work up ($NaBH_4$ in MeOH) gave (–)-**11**[9] ($[\alpha]_D$ –45.9° (c 1.0, $CHCl_3$); lit.,[9] $[\alpha]_D$ –46.4° (c 0.91, $CHCl_3$)) through concomitant β-elimination of acetoxy function during the reaction. The spectral data of (–)-**11** was identical with those in the literature.[9] Since absolute configuration of (–)-**11** was known as *R*, the stereochemistry of (–)-**7b** was determined to be 4*S*,5*R* at this stage. Assignment of stereostructure of (+)-**7a** was made by chemical correlation with (–)-**7b**; Deprotection (CF_3CO_2H, CH_2Cl_2) of *t*-butyl ether for (+)-**7a** followed by acetylation (Ac_2O, Py, DMAP) gave (–)-**7b**.

REFERENCES AND NOTES

1. S. Kano, T. Yokomatsu, and S. Shibuya, *J. Org. Chem.*, 1989, **54**, 513; S. Kano, T. Yokomatsu, and S. Shibuya, *Heterocycles*, 1990, **31**, 13.

2. D. Seebach, R. Imwinkelried, and T. Weber, 'Modern Synthetic Methods: EPG Synthesis with C,C Bond Formation via Acetal and Enamines', Vol. 4, ed. by R. Schefield, Verlag, 1986, pp.125-259.

3. All new compounds gave satisfactory elementary analyses and spectral data.

4. **5a**: mp 116-118 °C; δ (300 MHz, $CDCl_3$) 7.56-7.53 (2H, m), 7.42-7.31 (3H, m), 5.88 (1H, d, *J*=5.2 Hz), 4.62-4.57 (1H, m), 2.73 (1H, dd, *J*=17.5, 6.5 Hz), 2.62 (1H, dd, *J*=17.5, 4.7 Hz), 1.28 (9H, s); $[\alpha]_D$ −229° (c 0.5, $CHCl_3$) for (−)**5a**. **5b**: an oil for racemate, mp 83-84 °C for (−)-**5b**; δ (300 MHz, $CDCl_3$) 7.61-7.53 (2H, m), 7.32-7.27 (3H, m), 5.91 (1H, d, *J*=5.1 Hz), 5.72-5.66 (1H, m), 2.85 (1H, dd, J=18.1, 6.9 Hz), 2.68 (1H, dd, *J*=18.1, 4.1 Hz), 2.19 (3H, s); $[\alpha]_D$ −219.7° (c 0.74, $CHCl_3$) for (−)-**5b**. **6a**: mp 56-58 °C; δ (300 MHz, $CDCl_3$) 7.56-7.51(2H, m), 7.38-7.31(3H, m), 5.54(1H, d, *J*=2.9 Hz), 4.29-4.23 (1H, m), 2.61(1H, dd, *J*=18.0, 7.3 Hz), 2.42 (1H, dd, *J*=18.0, 3.4 Hz), 1.21 (9H, s). **6b**: an oil; δ (300 MHz, $CDCl_3$) 7.61-7.50(2H, m), 7.42-7.32(3H, m), 5.69(1H, d, *J*=0.6 Hz), 5.34(1H, br d, *J*=5.1 Hz), 2.58 (1H, dd, *J*=18.4, 6.3 Hz), 2.48 (1H, dd, *J*=18.4, 2.0 Hz), 2.10 (3H, s); $[\alpha]_D$+92.6° (c 0.5, $CHCl_3$) for (+)-**5b**.

5. Lactonization of chlorination product obtained from **2** gave corresponding *trans*-lactone predominantly (*cis*: *trans*=1:2) in 30% yield.

6. **7a**: an oil; δ (400 MHz, $CDCl_3$) 5.89-5.65 (1H, m), 5.25-5.15 (2H, m), 4.32 (1H, ddd, *J*=6.1, 5.9, 5.9 Hz), 4.06 (1H, ddd, *J*=7.4, 6.4, 6.1 Hz), 2.75 (1H, dd, *J*=17.7, 7.4 Hz), 2.49 (1H, dd, *J*=17.7, 6.4 Hz), 2.57-2.35 (2H, m), 1.18 (9H, s); $[\alpha]_D$ +62.1° (c 0.5, $CHCl_3$) for (+)-**7a**. **7b**: an oil; δ (300 MHz, $CDCl_3$) 5.85-5.7 (1H, m), 5.29-5.18 (2H, m), 5.16-5.11 (1H, m), 4.56 (1H, dt, *J*=6.1, 1.6 Hz), 2.92 (1H, dd, *J*=18.7, 7.1 Hz), 2.56 (1H, dd, *J*=18.7, 2.2 Hz), 2.48 (2H, br t, *J*=5.9 Hz), 2.10 (3H. s); $[\alpha]_D$ −17.3° (c 1.4, $CHCl_3$) for (−)-**7b**.

7. The stereochemistry of phenylthio group affected the reactivity for generation of radical species in case of 5-phenylthiooxazolidin-2-ones; S. Kano, T. Yokomatsu, and S. Shibuya, *Heterocycles*, 1990, **31**, 1711.

8. S. Sato, T. Hasegawa, M. Inaba, R. Nishida, T. Fujii, S. Nomizu, and T. Morikawa, *Chem. Lett.*, **1984**, 1389.

9. H. Suemune, M Hizuka, T. Kamashita, and K. Sakai, *Chem. Pharm. Bull.*, 1989, **37**, 1379.

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