



Pergamon

Tetrahedron Letters 41 (2000) 4189–4192

TETRAHEDRON
LETTERS

Highly stereoselective synthesis of enantiomerically pure β -hydroxy- γ -sulfinyl- γ -butyrolactone by asymmetric Pummerer type cyclization

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Received 7 February 2000; accepted 4 April 2000

Abstract

Enantiomerically pure *t*-butyl 4-sulfinyl-3-silyloxy-butanoate can be transformed stereoselectively in a Pummerer reaction with TFAA into the usual aldehyde or into a *cis* β -hydroxy- γ -sulfinyl- γ -butyrolactone. Experimental conditions allowing total control of the reaction in favor of either the aldehyde or the γ -butyrolactone are described. The corresponding methyl butanoate led, under the same conditions, only to the aldehyde. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: sulfoxides; Pummerer rearrangement; asymmetric induction; β -hydroxysulfoxides.

The well-known Pummerer rearrangement^{1,2} is a very useful transformation of a sulfoxide to the corresponding α -acetoxy sulfide,^{3,4} which is indeed a masked aldehyde. The most commonly used Pummerer reaction conditions require sodium acetate in refluxing acetic anhydride as the activating agent for the sulfoxide. In the case of thermally sensitive sulfoxides, trifluoroacetic anhydride (TFAA), another sulfoxide activating agent, provides almost spontaneously a mild Pummerer reaction at low temperature directly affording the corresponding aldehyde.⁵ In both cases, the reaction starts by the acylation of sulfoxide oxygen giving a trivalent sulfonium cation which is in equilibrium in the basic medium⁶ with the corresponding ylide. Finally, a rearrangement occurs at the α -position.

In a few cases an intramolecular Pummerer type cyclization reaction can take place. This was reported for the first time and independently by Allenmark and Stridsberg^{7,8} and Oae and Numata⁹ with a chirality transfer from sulfur to the adjacent carbon atom during the cyclization when an *ortho*-benzylsulfinyl benzoic acid was treated with DCC or Ac₂O. Later, Marino et al. reported the first example under Pummerer conditions of an intramolecular cycloaddition between a vinyl sulfoxide and dichloroketene. The stereoselectivity was dependent on the *E* or *Z* configuration of the vinylic component.^{10,11} β -Lactams were also obtained by ring closure of β -amid sulfoxides under Pummerer conditions with either

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TMSOTf¹² or *o*-silylated ketene acetals.^{13–16} In most of the cases the observed enantioselectivity for these cycloadditions was moderate (30 to 85%). A very highly enantioselective Pummerer type reaction was reported by Bravo:¹⁷ the cycloaddition of a *trans* vinyl sulfoxide to dichloroketene in Pummerer conditions (in presence of trichloroacetyl chloride) afforded a *trans* lactone in 98% enantiomeric excess via a [3,3]-sigmatropic rearrangement. Another report¹⁸ described the intramolecular lactonization of 3-alkyl-4-phenylsulfinylbutanoic acid in Ac₂O/*p*TsOH) with predominant *trans* configuration (87:13) in 43% yield.

We report now the first highly diastereoselective formation (*de* >98%) of a *cis*-β-hydroxy-γ-sulfenyl-γ-butyrolactone under mild intramolecular Pummerer type conditions.

We recently described the stereocontrolled synthesis of the C1–C13 fragment of nystatin A.¹⁹ The preparation of the β-hydroxysulfoxide (–)-**1** has already been described^{19–21} as well as the classical Pummerer reaction¹⁹ of (–)-**1** with Ac₂O, AcONa giving the corresponding α-acetoxysulfide **2** which was then transformed into the aldehyde **3** in three steps to avoid any racemization of the chiral center (Raney nickel desulfurization, DIBAL-H reduction of the acetate and Swern oxidation of the resulting alcohol). In order to obtain a one-pot transformation of sulfoxide (–)-**1** into aldehyde **3** under very mild conditions we used the classical TFAA-2,4,6-collidine Pummerer conditions.⁵ At 0°C we obtained the expected and known¹⁹ aldehyde **3** but also lactone **4** in about the same amount (52:48, Table 1, entry 1 and Scheme 1). Lactone **4** was shown by ¹H and ¹³C NMR²⁴ to be a single diastereomer with the *cis* configuration (NOE and ROESY between H₄ and H₅) and therefore with the 4*R*,5*R* configuration (the 4*R* configuration being maintained during the reaction).

Table 1
Base and temperature effects on the Pummerer reaction of sulfoxide (–)-(3*R*,5*S*)-**1**

Entry	TFAA Eq.	Base (eq)	T°C ^a	Reaction time	Product ratio ^b (+)- 3 : (+)- 4
1	10	Collidine (6)	0	30 min	52 : 48
2	10	Collidine (6)	-40	3 h	73 : 27
3	5	Collidine (5)	30 to RT	2h 30	35 : 65
4	6	Collidine (6)	-75 to -35	22 h	90 : 10
5	3	CF ₃ CO ₂ Na (3)	0	20 min	13 : 87
6	3	CF ₃ CO ₂ Na (10)	-30 to RT	30 min	4 : 96

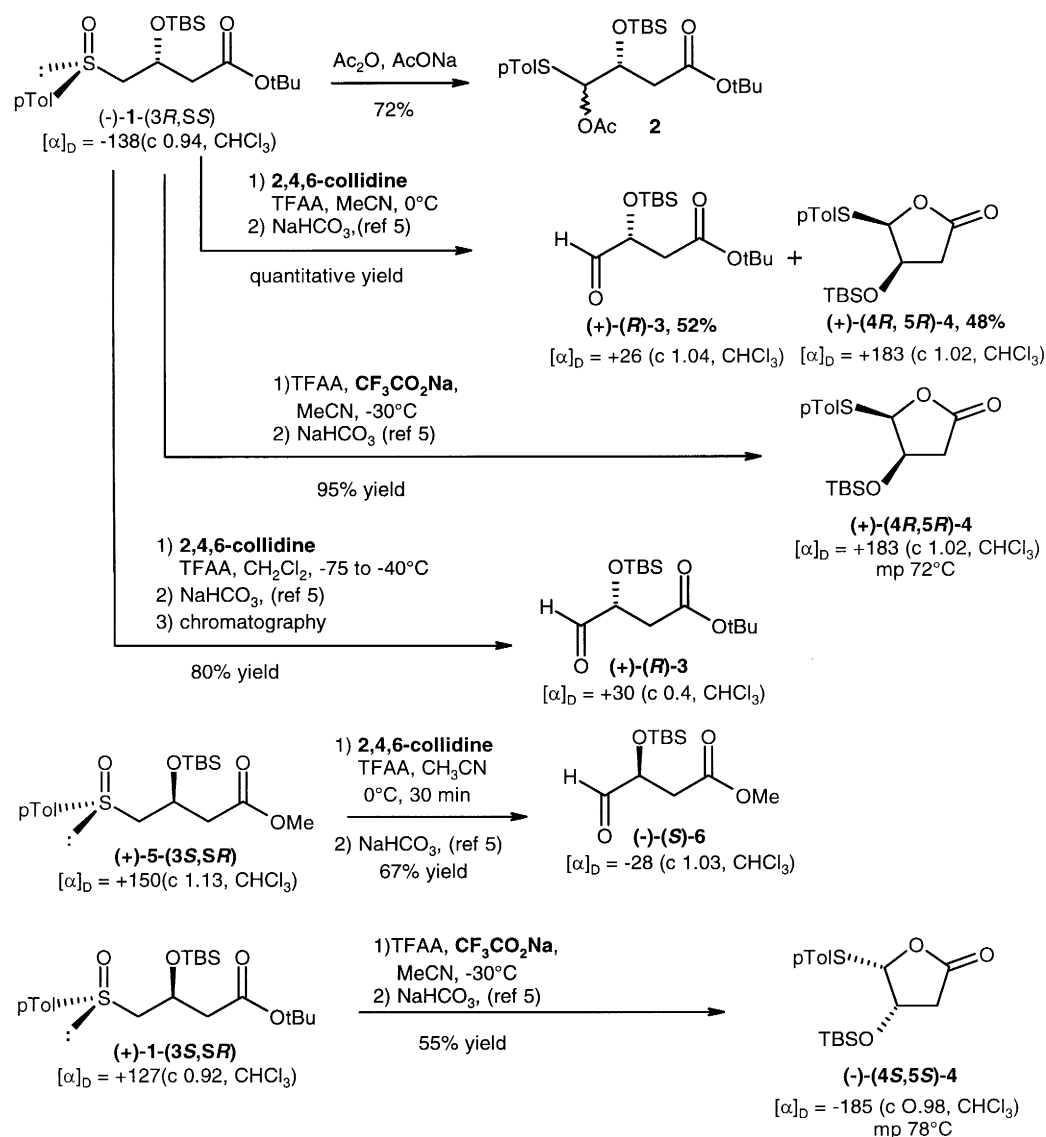
a) reactions above –40°C were carried out in dry acetonitrile, below –40°C dry dichloromethane was used ; b) by NMR on the crude product.

It was shown that in the presence of collidine it was possible to preferentially obtain aldehyde **3** by lowering the temperature: between –75 and –35°C the reaction was slow but gave 90% of **3** (entry 4). When using sodium trifluoroacetate as base the proportion of lactone **4** was as high as 96% in quantitative yield (entry 6).

Starting from the enantiomeric, (+)-**1**-(3*S*,5*R*), the enantiomeric lactone (–)-(4*S*,5*S*)-**4**²⁴ was obtained in the presence of sodium trifluoroacetate (Scheme 1).

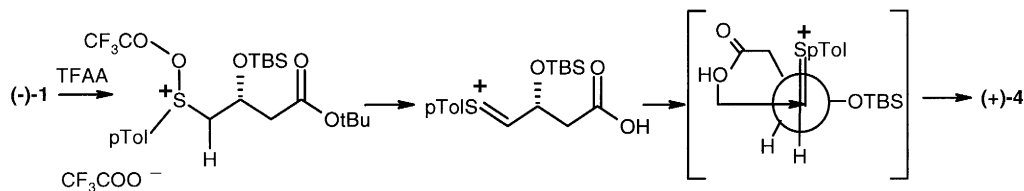
Finally, we observed that the methyl ester (+)-(3*S*,5*R*)-**5** in presence of collidine afforded only the corresponding aldehyde (–)-(5)-**6** in 67% yield instead of the mixture of aldehyde and lactone we got from the *t*-butyl ester (Scheme 1).

From this last result it is reasonable to assume that in the Pummerer reaction with TFAA, the *t*-butyl ester is hydrolyzed under these acidic conditions with formation of isobutene. The resulting



Scheme 1.

carboxylic acid can then add to the highly polarized carbon sulfur double bond^{22,23} to give lactone **4**, the stereoselectivity following the Felkin Anh model (Scheme 2). On the contrary, the methyl ester was not hydrolyzed during the Pummerer reaction and only the aldehyde was obtained.



Scheme 2.

In conclusion, we have shown that enantiomerically pure *t*-butyl 4-sulfinyl-3-silyloxybutanoate can be

transformed stereoselectively in a Pummerer reaction with TFAA into the usual aldehyde or into a *cis* β -hydroxy- γ -sulfenyl- γ -butyrolactone. We describe the experimental conditions allowing total control of the reaction in favor of either the aldehyde or the γ -butyrolactone. The corresponding methyl butanoate led only to the aldehyde.

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24. Analytical data of (+)-**4**: $[\alpha]_D^{25} = +183$ (*c* 1.02, CHCl₃); m.p.=72°C; ¹H NMR (CDCl₃): 7.44 (A of (AB)₂, 2H, pTol, J_{AB}=8 Hz, $\Delta\nu$ =62 Hz), 7.13 (B of (AB)₂, 2H, pTol, J_{AB}=8 Hz, $\Delta\nu$ =62 Hz), 5.69 (d, 1H, H-5, J=4 Hz), 4.74–4.67 (m, 1H, H-4), 2.65 (AB of ABX, 2H, H-3, J_{AB}=17 Hz, J_{AX}=5.5 Hz, J_{BX}=3 Hz, $\Delta\nu$ =33.5 Hz), 2.33 (s, 3H, CH₃-Ar), 0.95 (s, 9H, Si*t*Bu), 0.20 (s, 3H, SiMe), 0.14 (s, 3H, SiMe). ¹³C NMR (CDCl₃): 174.0 (CO-2), 138.3 (C arom), 132.7 (CH arom), 130.0 (CH arom), 129.7 (C arom), 94.6 (CH-5), 70.5 (CH-4), 39.2 (CH₂-3), 25.8 (CH₃, *t*Bu), 21.2 (CH₃, pTol), 18.3 (C, *t*Bu), -4.7 (CH₃, SiMe), -4.9 (CH₃, SiMe). Anal calcd for C₁₇H₂₆O₃SiS (338.54): C, 60.31; H, 7.74; found: C, 60.49; H, 7.95. Analytical data of (-)-**4**: $[\alpha]_D^{25} = -185$ (*c* 0.98; CHCl₃); m.p.=78°C.