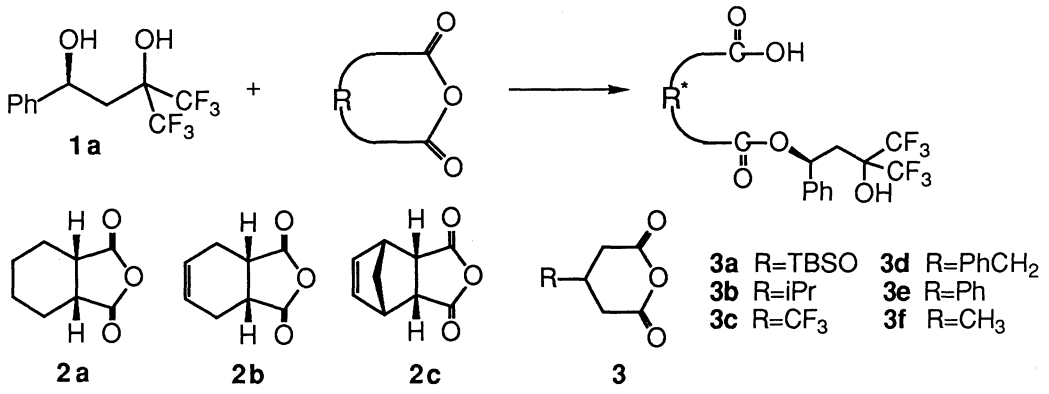
CHEMISTRY LETTERS, pp. 389-392, 1992.

Highly Diastereoselective Alcoholysis of σ-Symmetric Dicarboxylic Acid Anhydrides Using 1-Phenyl-3,3-bis(trifluoromethyl)propan-1,3-diol

Yoshimitsu SUDA, Seiji YAGO, Motoo SHIRO,† and Takeo TAGUCHI*
Tokyo College of Pharmacy, 1432-1 Horinouchi, Hachioji, Tokyo 192-03
†Rigaku Corporation, 3-9-12 Matsubara, Akishima, Tokyo 196

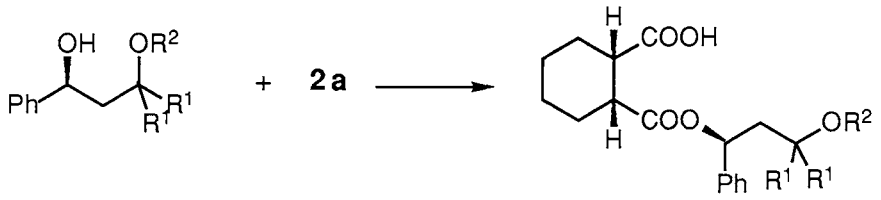
Highly diastereoselective alcoholysis of σ-symmetric dicarboxylic acid anhydrides was performed using 1-phenyl-3,3-bis(trifluoromethyl)propan-1,3-diol. The importance of the geminally trifluoromethylated carbinol moiety for achieving a high degree of chiral induction was confirmed from lower diastereoselectivity with the hydroxyl protected 1,3-diol or with the similar 1,3-diols having hydrocarbon substituents instead of the trifluoromethyl group.

Chiral differentiation of two identical carboxyl groups in a σ–symmetric dicarboxylic acid should be an important strategy in organic synthesis, since the chiral product thus obtained can serve as an intermediate for further selective transformation of these functional groups into both enantiomeric series.[1] For this purpose, both enzymatic and chemical approaches have been extensively investigated.[2,3] However, enzymatic methods are sometimes hampered by unpredictable specificity to the structures of substrates used and the quality of the enzyme itself.[4,5] Among nonenzymatic procedures reported so far, some have been found useful for synthetic reactions based on the degree of chiral induction achieved and/or reaction conditions.[3,6] A convenient and efficient method for preparing chiral compounds from a variety of symmetric dicarboxylic acid anhydrides is thus still desirable. In this paper, we report highly diastereoselective alcoholysis of σ–symmetric cyclic dicarboxylic acid anhydrides **2** and 3-substituted glutaric anhydrides **3** into the half-esters using 1-phenyl-3,3-bis(trifluoromethyl)propan-1,3-diol **1a**.



At first, we carried out chiral alcoholysis of *cis*-cyclohexan-1,2-ylene bis(carboxylic acid) anhydride **2a** with (*S*)-1-phenyl-3,3-bis(trifluoromethyl)propan-1,3-diol **1a**[7] or with other 1,3-diols **1b-1d** to examine

the effects of reaction conditions and substituents on diastereoselectivity (Table 1). From these results the followings are noteworthy: 1) With sodium salt of the geminally bistrifluoromethylated 1,3-diol **1a**, the reaction was completed within a short period as compared with those with other 1,3-diols (Runs 1-4 vs. Runs 5-9). 2) High diastereoselectivity was achieved in nonpolar solvent such as toluene (96:4, Run 1); by increasing the polarity of the solvent, the diastereoselectivity decreased (Runs 1-3). 3) Addition of 1 mol equiv. of 15-crown-5 caused no chiral induction (Run 4). 4) On using Et_2Zn as a base in THF, the direction of chiral induction was opposite to that in toluene (Runs 5, 6). 5) When the tertiary hydroxyl group of the fluorinated 1,3-diol **1a** was protected as its methyl ether **1b**, both the efficacy of the reaction and diastereoselectivity of the product extremely diminished (Run 7). 6) With similar 1,3-diols having hydrocarbon substituents (**1c** and **1d**) instead of trifluoromethyl group, chiral induction was extremely lower than that with **1a** under similar reaction conditions (Runs 8, 9).

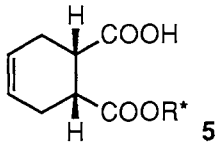


1a R^1=CF_3 R^2=H **1c** R^1=Me R^2=H **4a** R^1=CF_3 R^2=H **4c** R^1=Me R^2=H
1b R^1=CF_3 R^2=Me **1d** R^1=Ph R^2=H **4b** R^1=CF_3 R^2=Me **4d** R^1=Ph R^2=H

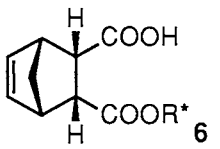
Table 1. Chiral Alcoholysis of **2a** with 1-Phenyl-1,3-diol **1**

Run	1,3-Diol	Base	Solvent	Temp/°C	Time/h	4	Yield/%[a]	Ratio[b]	Config.[c,d]
1	**1a**	NaH	Toluene	-78	1	**4a**	94	96 : 4	1*R*,2*S*
2	**1a**	NaH	THF	-78	1	**4a**	95	87 : 13	1*R*,2*S*
3	**1a**	NaH	CH_3CN	-78	1	**4a**	96	50 : 50	---
4	**1a**	NaH[e]	Toluene	-78	1	**4a**	94	50 :50	---
5	**1a**	Et_2Zn	Toluene	0	24	**4a**	58	78 : 22	1*R*,2*S*
6	**1a**	Et_2Zn	THF	0	24	**4a**	56	33 : 67	1*S*,2*R*
7	**1b**	NaH	Toluene	rt	24	**4b**	36	54 : 46	1*R*,2*S*
8	**1c**[f]	NaH	Toluene	-78	12	**4c**	98	60 : 40	---[g]
9	**1d**[f]	NaH	Toluene	-78	7	**4d**	quant.	55 : 45	---[g]

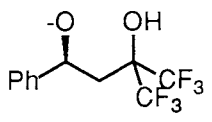
a) Isolated yield. b) Determined by ^{1}H-NMR (400 MHz) after conversion to the methyl ester by treating **4** with diazomethane. c) Determined by comparison of the optical rotation value of the corresponding γ-lactone derived from **4** with the reported value.[8,9] d) Configuration of major isomer is shown. e) 15-Crown-5 (1mol equiv.) was added. f) Racemic 1,3-diol was used. g) Not determined.



5

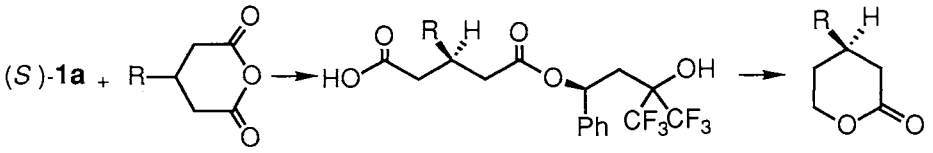


6

-OR* = 

Similarly, high diastereoselectivites in alcoholysis of the anhydrides **2b**, **2c** with (*S*)-**1a** in the presence of sodium hydride in toluene leading to **5** (92% de, 1*R*,2*S*) and **6** (74% de, 2*R*,3*S*), respectively were observed.[8,9] The bis(trifluoromethyl)hydroxymethyl moiety may thus play an important role for achieving high diastereoselectivity within a short reaction time.[10]

The chiral alcoholysis of 3-substituted glutaric anhydrides (**3a-3f**) with **1a** proceeded with moderate to high diastereoselectivity depending on the steric size of the substituent (R in **3**). Results are summarized in Table 2. In this case, sodium hydride was effective as a base for achieving high selectivity within a short reaction period.[11]. With the glutaric anhydride having a more sterically bulky substituent, higher chiral induction was realized. For example, isopropyl derivative **3b** and trifluoromethyl derivative **3c** resulted in similarly high diastereomer ratio (95 : 5 in both cases),[12] while lower ratio (83 : 17) was obtained with methyl derivative **3f** (Runs 2, 3,and 6). In all cases, the direction of chiral induction was the same giving the half-esters of *R*-configuration as long as (*S*)-1,3-diol **1a** was used. Compared with enzymatic approaches to these chiral molecules,[5] the present reaction may possibly indicate a certain generality since the configuration of the product and the degree of chiral induction appear predictable.



3 **7** **8**

Table 2. Chiral Alcoholysis of 3-Substituted Glutaric Anhydride **3** with (*S*)-**1a**[a]

Run	R in **3**		**7**	Yield/%[b]	Ratio[c]	Configuration[d]
1	TBSO	**3a**	**7a**	90	96 : 4	3*R*,1'*S*[e]
2	i-Pr	**3b**	**7b**	94	95 : 5	3*R*,1'*S*[f]
3	CF_3	**3c**	**7c**	95	95 : 5	3*R*,1'*S*[g]
4	$PhCH_2$	**3d**	**7d**	96	88 : 12	3*R*,1'*S*[f]
5	Ph	**3e**	**7e**	95	83 : 17	3*R*,1'*S*[f]
6	CH_3	**3f**	**7f**	90	83 : 17	3*R*,1'*S*[f]

a) Reaction conditions: NaH, toluene, -78 °C, 15-20 min. b) Isolated yield. c) Determined by ^{1}H-NMR (400 MHz) after conversion to the methyl ester by treating **7** with diazomethane. d) Configuration of major isomer is shown. e) Determined by comparison of the optical rotation value of the adamantanamine salt of monomethyl ester derived from **7a** [1) diazomethane, 2) hydrogenolysis, 3) adamantanamine] with the reported value.[13] f) Determined by comparison of the optical rotation value of the corresponding δ–lactone **8** derived from the half ester **7** [1) BH_3•DMS, 2) *p*-TsOH] with the reported values.[5] g) See Ref. 14.

In conclusion, alcoholysis of σ-symmetric dicarboxylic acid anhydride with the geminally bistrifluoromethylated 1,3-diol **1a** proceeds efficiently to give the half-ester in a highly diastereoselective manner.

We are grateful to Tokuyama Science Foundation for financial support.

References

1) Y. Nagao and E. Fujita, *Yuki Gousei Kagaku Kyoukaishi*, **42**, 622 (1984).

2) M. Ohno and M. Otsuka, *Org. React.*, **37**, 1 (1989) and references cited therein.

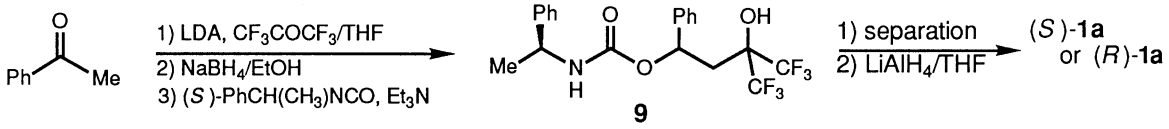
3) Some representative reports: T. Rosen and C. H. Heathcock, *J. Am. Chem. Soc.*, **107**, 3731 (1985); P. D. Theisen and C. H. Heathcock, *J. Org. Chem.*, **53**, 2374 (1988); M. Ohtani, T. Matsuura, F. Watanabe, and M. Narisada, *ibid.*, **56**, 2122, 4120 (1991).

4) E. J. Toone, M. J. Werth, and J. B. Jones, *J. Am. Chem. Soc.*, **112**, 4946 (1990).

5) For example: L. K. P. Lam, R. A. H. F. Hui, and J. B. Jones, *J. Org. Chem.*, **51**, 2047 (1986).

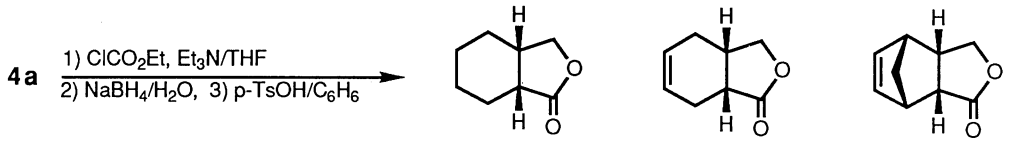
6) M. Ohshima and T. Mukaiyama, *Chem. Lett.*, **1987**, 377; Y. Nagao, Y. Hagiwara, Y. Hasegawa, M. Ochiai, T. Inoue, M. Shiro, and E. Fujita, *ibid.*, **1988**, 381.

7) Both enantiomers of **1a** were readily prepared in optically pure form through silica gel column chromatographic separation of the carbamate **9** derived from (*S*)-*N*-α-methylbenzylisocyanate as shown below. The absolute stereochemistry was confirmed by X-ray crystallographic analysis of (1*S*, 1'*S*)-isomer of **9** (mp 121.5-122 °C). (*S*)-**1a**: $[\alpha]_D^{25}$ -60.48° (c 1.47, $CHCl_3$); (*R*)-**1a**: $[\alpha]_D^{25}$ +60.44° (c 1.25, $CHCl_3$).



9

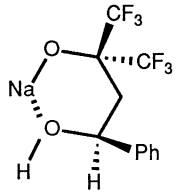
8) Conversion of the half-ester **4a** to the γ-lactone **10** was carried out as shown below. No racemization of the recovered alcohol **1a** could be detected. In a similar manner, **5** and **6** were converted to the γ-lactone **11** and **12**, respectively.



10 11 12

9) H.-J. Gais and K. L. Lukas, *Angew. Chem., Int. Ed. Engl.*, **23**, 142 (1984); S. Takano, K. Inomata, A. Kurotaki, T. Ohkawa, and K. Ogasawara, *J. Chem. Soc., Chem. Commun.*, **1987**, 1720.

10) As an expected characteristic property of the 1,3-diol **1a**, enhanced acidity of the hydroxyl group adjacent to the trifluoromethyl group may cause the internal coordination of the another hydroxyl oxygen to the counter cation (Na^+) bound to the more acidic hydroxyl group to form the rigid six-membered ring structure, which may contribute to lead to the effective chiral induction.

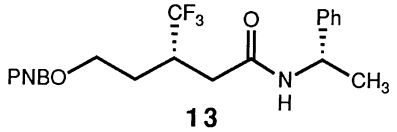


11) Reaction of **3a** with (*S*)-**1a** using Et_3N as a base instead of NaH in toluene at 0 °C required for 1 day to give **7a** in 50% de (98% chemical yield).

12) For discussion of steric effect of trifluoromethyl group, see: G. Bott, L. D. Field, and S. Sternhell, *J. Am. Chem. Soc.*, **102**, 5618 (1980).

13) D. S. Karanewsky, M. F. Malley, and J. Z. Gougoutas, *J. Org. Chem.*, **56**, 3744 (1991).

14) The absolute configuration of **7c** was determined by X-ray crystallographic analysis of the *p*-nitrobenzoate of the hydroxyamide **13** derived from the minor diastereomer of **7c**.



13

(Received December 16, 1991)