Desymmetrization of *meso*-Diols by Acylation with Axially Chiral Twisted Amides and Its Mechanistic Studies

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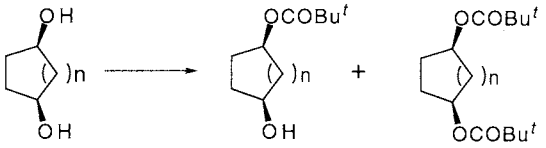
Desymmetrization of *meso*-1,2-, -1,3-, and -1,4-diols was performed by acylation with chiral twisted amides.[1] The conformation of the twisted amides was studied by optimization of the PM3 method in order to elucidate the reaction mechanism. The directionality of the amide bond rotation was considered to be significantly responsible for the stereoselectivity.

Desymmetrization of *meso*-diols by way of enzymatic acyl transfer reaction is an established powerful method for the preparation of chiral alcohols,[2] which has been applied to a number of natural product syntheses. Recently, non-enzymatic methods have also been extensively explored.[3] Most non-enzymatic desymmetrization processes of diols by acylation are conducted at very low temperature or in the presence of metal salts for chelation control to achieve high stereoselectivity; however, few examples for the reactions which are conducted under neutral and mild conditions without any metal salts such as enzymatic reactions have been reported.

Previously, we have reported that chiral twisted amides serve as stereoselective acylating agents for racemic *sec*-alcohols under neutral conditions.[4] Here we report a new method for the desymmetrization of several diols (Scheme 1) and describe its possible reaction mechanism where axial chirality of the amide moiety is a dominant factor in controlling the stereoselectivity.



Scheme 1.

Desymmetrization of *meso*-1,2-, -1,3-, and -1,4-diols **5-8** with twisted amides **1-4** as acylating agents was investigated. The results are summarized in Table 1. Although 1,2- and 1,3-diols have often been employed as substrates for the non-enzymatic desymmetrization, there are few examples of the use of *sec-meso*-1,4-diols. The reactions of *cis*-tetrahydronaphthalene-1,4-diol (**6**) with 1.1 eq of amides **1-4** in toluene at 80 °C for 20 h gave the corresponding monopivalate in good yields (entries 1-4). The enantiomeric excess was determined by HPLC analysis using a chiral column. Among the amides, **3** and **4** are more effective for the stereoselective acylation than **1** and **2**. Addition of triethylamine enhances the reaction rate sufficiently to proceed even at room temperature with higher selectivity than that at 80 °C (entry 5); however, amide **4** is less reactive than **3** at rt. Addition of DMAP decreases the enantioselectivity, although it very effectively accelerates the reaction rate (entry 6). THF is also effective accompanied with a slight decrease of selectivity (entry 7). The selectivity for the desymmetrization of *cis*-1,3-indandiol (**5**) with **3** is lower than that observed for 1,4-diol **6** (entry 8),

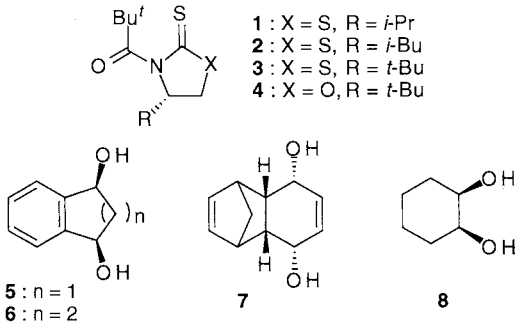


Table 1. Desymmetrization of *meso*-diols **5-8** with twisted amides **1-4**[a]

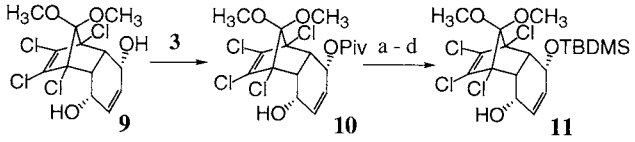
Entry	Amide	Diol	Temp/°C	Time/h	Monoester/%	ee[b]/%	Diester/%
1	**1**	**6**	80	20	71[c]	71	27[c]
2	**2**	**6**	80	20	69[d] (52)[c]	48	21[d]
3	**3**	**6**	80	20	79[c]	79	17[c]
4	**4**	**6**	80	20	69[c]	78	28[c]
5	**3**	**6**[e]	rt	138	98[d] (34)[c]	88	0
6	**3**	**6**[f]	rt	48	84[c]	51	0
7	**3**	**6**[g]	rt	71	99[d] (41)[c]	82	0
8	**3**	**5**	80	14	78[c]	33	8[c]
9	**3**	**7**	80	14	92[d] (68)[c]	44	0
10	**4**	**7**	80	14	61[d] (23)[c]	34	11[d]
11	**3**	**7**[e]	50	89	86[d] (37)[c]	56	0
12	**3**	**8**	80	15	86[d] (55)[c]	42[h]	0

[a]The reactions were conducted in toluene unless otherwise noted. [b]*S* configuration. [c]Isolated yield. [d]Conversion yield. [e]Et_3N (2 eq) was added. [f]DMAP (2 eq) was added. [g]THF was used as a solvent in the presence of Et_3N (5 eq). [h]The ee was determined by ^1H NMR in the presence of $Eu(hfc)_3$ and the absolute configuration is not determined.

which indicates that the stereoselectivity is significantly dependent on the structure of the diols employed. The absolute configurations of the monoesters were determined by conversion to the known 1-tetralol and 1-indanol. Acylation of diol **7** with **3** and **4** at 80 °C gave the reported (*S*)-monopivalate[5] in 44% and 34% ee, respectively (entries 9 and 10). Lowering the reaction temperature increases the selectivity to 56% ee (entry 11). Such chiral monoesters of diol **7** obtained by enzymatic desymmertrization have been proved to be useful building blocks for natural product synthesis.[6] This method was also applicable to a saturated 1,2-diol **8** similar to the 1,3- and 1,4-diols (entry 12).

meso-1,4-Diol **9** has been used as a starting material for the synthesis of a macrolide antibiotic nodusmicin and its analog 18-deoxynargenicin.[7] In the synthesis it has been reported that attempts to generate the chiral monoacetate by esterification of **9** or hydrolysis of the diacetate of **9** with several enzymes failed. This result prompted us to study the desymmetrization of **9** by

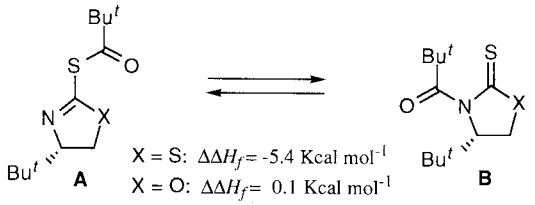
the present method. When diol **9** and 1.1 eq. of amide **3** in heptane were heated at refluxing temperature for 96 h, (*R*)-monoester (**10**) (61% ee) and diester were produced in 45% and 53% conversion yields, respectively. Determination of the absolute configuration was performed by deriving **10** to the reported monosilyl ether **11**,[7] which is the intermediate for the synthesis of nodusmicin and 18-deoxynargenicin, in the following manner as described in Scheme 2. After protection of the hydroxy group of **10** with ethyl vinyl ether, hydrolysis of the pivalate gave a hydroxyether in 78% yield. Protection of the resulting hydroxy group with *tert*-butyldimethylsilyl triflate and deprotection of the ethoxyethyl ether moiety yielded alcohol **11** (48%), the optical rotation of which was compared with the literature.



Reagent: (a) ethylvinyl ether, PPTS, CH_2Cl_2; (b) 2N NaOH, MeOH; (c) TBDMSOTf, 2,6-lutidine, DMF; (d) PPTS, MeOH.

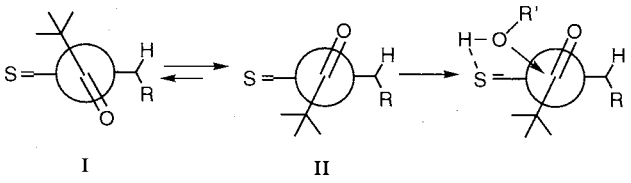
Scheme 2.

The mechanism for the desymmetrization was studied by taking advantage of PM3 optimizations for conformation of the twisted amides.[8] As we previously reported, **3** is a 25:1 mixture of *S*-acyl form **A** and *N*-acyl form **B** in solution, whereas **4** is a 1:12 mixture of **A** and **B** forms.[4] This surprisingly large difference in the preference between **A** and **B** forms in solution despite the small difference in their framework structures was successfully explained by the comparison of ΔH_f values of **A** and **B** forms (Scheme 3). Thus, the $\Delta\Delta H_f$ value (ΔH_{fA}-ΔH_{fB}) of **3** (X=S) is significantly lower than that of **4** (X=O), indicating thermodynamic preference of the *S*-acyl form in **3**. The reaction would nevertheless proceed from **B** form, because the chiral center and the carbonyl group of **A** form are too apart from each other to discriminate between the two hydroxy groups of *meso*-diols. Moreover, the selectivity for the desymmetrization reaction with **3** is close to that with **4** (entries 3 and 4).



Scheme 3.

There would be two rotamers **I** and **II** for the *N*-pivaloyl form **B** as shown in Scheme 4. The preference in the rotamers is also predicted by considering the ΔH_f values. The heats of formation of the optimized rotamer **I** and **II** of **1-4** estimated by the PM3 method are listed in Table 2. For all amides the values of rotamer **II** are lower than those of **I**, indicating the thermodynamic preference of rotamer **II**. Reported X-ray geometry of amide **2**[9] also supports the preference of the rotamer **II**. Since the twisted amides have higher energy than the planar ones because of loss in resonance energy and the twisted structures are very close to the transition structures of alcoholysis of the amides,[10] the rotamer ratios in the transition state may be reflected by those in the ground state; therefore, the acylation reactions would proceed from the rotamer **II**.[11] The stereoselectivity of amides **1-4** for *meso*-diols is also considered to be related to their rotamer ratios: The $\Delta\Delta H_f$ value for the least selective amide **2** is the lowest among them.



Scheme 4.

Table 2. Heats of formation for rotamers **I** and **II** estimated by PM3 method, and their difference $\Delta\Delta H_f$

Amide	ΔH_f / Kcal mol^{-1}		$\Delta\Delta H_f$ / Kcal mol^{-1}
	Rotamer **I**	Rotamer **II**	
1	-29.2	-32.6	3.4
2	-36.5	-38.1	1.6
3	-31.7	-34.9	3.2
4	-78.1	-80.6	2.5

These studies suggest that the role of the asymmetric center at the 4-position controls the directionality of the amide bond twisting to produce axial chirality, which enables discrimination of the two hydroxy groups of *meso*-diols in the 6-membered transition state as shown in Scheme 4.

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References and Notes

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