Asymmetric Acylation of *sec*-Alcohols with Twisted Amides Possessing Axial Chirality Induced by the Adjacent Asymmetric Center

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This paper reports that axially chiral twisted amides serve as asymmetric acylating agents for *sec*-alcohols under neutral conditions. Kinetic resolution of various racemic *sec*-alcohols and desymmetrization of 1,2-, 1,3-, and 1,4-*meso*-diols were performed by using the twisted amides. The utility of this desymmetrization method was shown by the preparation of the synthetic intermediate **28** for macrolide antibiotic nodusmicin and 18-deoxynargenicin. The stereoselectivity of the acylation reactions is significantly dependent on the bulkiness of both the acyl group and the C-4 substituent of the chiral auxiliary. When an amide possessing an imidazolyl group at C-4 was employed, the stereoselectivity was reversed to give *R* esters. A possible working model of the acylation reaction is also described on the basis of the structural studies of the twisted amides by IR and ^{1}H and ^{13}C NMR spectroscopies and AM1 calculations. These studies suggested that rotamer **II** is thermodynamically more stable than the others. The rotamer **II** has an axial chirality about its C(O)−N linkage that is induced by the adjacent chiral center. This would enable discrimination of the two enantiomeric hydroxy groups of the racemic alcohols or *meso*-diols.

Introduction

Kinetic resolution of racemic *sec*-alcohols and desymmetrization of *meso*-diols by way of acyl transfer reactions are effective methods for obtaining chiral alcohols. To achieve asymmetric acylation, enzymatic processes have widely been used as the most effective approach[1] and have been applied to the preparation of a number of natural products and bioactive compounds. However, since the substrate specificity of enzymes is very high, as a result, structural variation of the substrates is often limited. Recently, nonenzymatic methods have also been extensively explored.[2−4] While most nonenzymatic asymmetric acylations are conducted at very low temperature or in the presence of a metal salt for chelation control to achieve high stereoselectivity, recent efforts have enabled the acylation under very mild conditions.[3a,h−j]

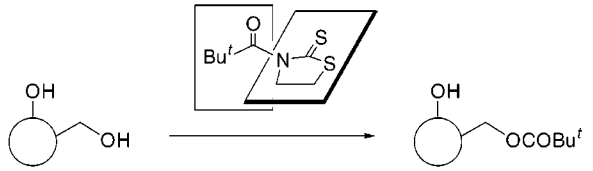

Figure 1. Reported selective acylation of diols with a twisted amide.

Previously, we have reported that 3-pivaloyl-1,3-thiazolidine-2-thione possessing an extremely twisted amide linkage[5,6] serves as a selective acylating agent for diols having primary and secondary hydroxy groups and those having alcoholic and phenolic hydroxy groups under neutral conditions (Figure 1).[7] In the course of our studies on the structure and reactions of twisted amides, we were interested in the asymmetric acylation by utilizing axially chiral twisted amides. If it is possible to control the directionality of the amide bond twisting, axial chirality will be induced in the C(O)−N bond (Figure 2). The axially chiral twisted amides seem to discriminate enantiomeric hydroxy groups during the acylating process and would serve as asymmetric acylating agents. Although the imides and amides possessing axial chirality about the C−N[8] and C−C(O)[9] bonds have recently received

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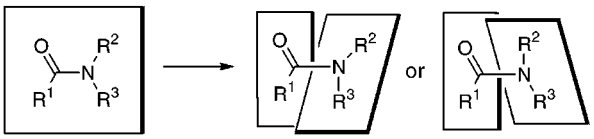


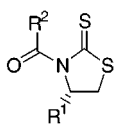
Figure 2. Generation of axial chirality by amide bond twisting.

considerable attention in various asymmetric synthesis, little is known about axial chirality based on the C(O)−N bond.

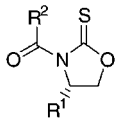
In this paper, we report that twisted amides **1**−**8**, which have axial chirality about the C(O)−N bond induced by the adjacent asymmetric center, serve as asymmetric acylating agents for racemic *sec*-alcohols and *meso*-diols.[10] Furthermore, a possible working model in the acylating process was proposed by studying the conformational structures of these amides on the basis of the IR and ^{1}H and ^{13}C NMR spectral data and AM1 calculations.

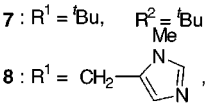
Results and Discussion

Amides **1**−**8** were readily prepared by the acylation of the corresponding (*S*)-4-isopropyl-,[11] (*S*)-4-isobutyl-,[12] (*S*)-4-*tert*-butyl-,[7] and (*S*)-4-benzyl-1,3-thiazolidine-2-thiones and (*S*)-4-*tert*-butyl-[7] and (*S*)-4-(3-methyl-3*H*-imidazol-4-yl)-1,3-oxazolidine-2-thiones,[13] which were synthesized from L-amino acids via several steps.



1 : R^1 = ^{t}Bu, R^2 = Me
2 : R^1 = ^{t}Bu, R^2 = ^{i}Pr
3 : R^1 = ^{t}Bu, R^2 = ^{t}Bu
4 : R^1 = ^{i}Pr, R^2 = ^{t}Bu
5 : R^1 = ^{t}Bu, R^2 = ^{t}Bu
6 : R^1 = Bn, R^2 = ^{t}Bu



7 : R^1 = ^{t}Bu, R^2 = ^{t}Bu
8 : R^1 =  , R^2 = ^{t}Bu

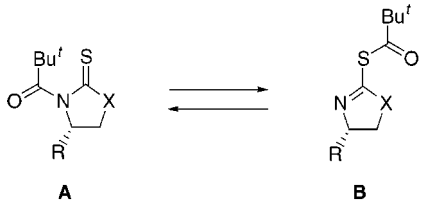
The structures of the amides **1**−**8** were studied by ^{1}H and ^{13}C NMR and IR spectroscopies. The data are shown in Table 1. The carbonyl stretching bands of the amides **1** and **2** are observed at 1696−1697 cm^{-1}. On the other hand, those of **3**−**8** having a pivaloyl group appear at 1720−1739 cm^{-1} in solid or neat film, indicating that these amide linkages are highly twisted compared to those of **1** and **2**.[5,12] When they are measured in $CHCl_3$, only the carbonyl stretching band of **3** dramatically shifted to lower frequency and was observed at 1700 cm^{-1}. In the ^{13}C NMR spectra, the carbonyl and thiocarbonyl carbons of the amides except for amide **3** were observed between δ170.3−189.0 and δ184.8−205.3, respectively. The $\Delta\delta^{13}$C values, which were determined by comparing with those of the corresponding standard *N*-acylpyrrolidines[14] in order to evaluate the net twisting effect, clearly show that the $\Delta\delta^{13}$C values of **4**−**8** were much higher than those of **1** and **2**. This also supports the significant amide bond twisting of **4**−**8**.

Table 1. IR (cm^{-1}) and ^{1}H and ^{13}C NMR (ppm) Spectral Data for 1−8

amide	νC=O[a]	δ^1H_4[b]	δ^{13}C=O[c]	δ^{13}C=S[c]	$\Delta\delta^{13}$C=O[c]	ratio (A/B)[b]
1	1697	5.31	170.3	205.3	1.2	
2	1696	5.38	177.9	204.6	2.2	
3	1739 (1700)[d]	4.15[e]	201.6	158.8[f]		1:25[e]
4	1737 (1726)[d]	4.55	188.3	200.8	11.9	6:1[g]
5	1720 (1727)[d]	4.55−4.61	189.0	200.1	13.6	11:1
6	1720	4.65	188.6	200.1	12.2	17:1
7	1734 (1730)[d]	4.44−4.59[g]	184.8	187.6	8.4	12:1[g]
8	1734	4.60−4.66	184.2	186.2	7.8	

[a] KBr disk. [b] 400 MHz in $CDCl_3$ unless otherwise noted. [c] 100.4 MHz in $CDCl_3$. [d] In $CHCl_3$. [e] In $C_6D_5CD_3$. [f] This value is not for C=S, but for C=N. [g] In C_6D_6.

Scheme 1



A **B**

^{1}H NMR spectra show that **1**, **2**, and **8** exist as a single isomer, whereas **3**−**7** are a mixture of two structural isomers, which are considered to be the *N*-acyl form **A** and the *S*-acyl form **B** as shown in Scheme 1. The isomer ratio was determined by the ^{1}H NMR spectra on the basis of the integration of H-3 and H-4. These isomers are not considered to be rotamers because the rotational barrier of this type of compound is generally very small; for example, the rotational barrier of diacetylamine is about 10.8 kcal/mol.[15] The ^{13}C NMR and IR spectral data of the major isomer satisfied the twisted amide structure as described above; the δ^{13}C values of the carbonyl and thiocarbonyl carbons and the νC=O values of **4**−**7** are close to those of reported, structurally analogous twisted amides.[5] The structure of amide **5** has already been confirmed to be the *N*-acyl form **A** by X-ray analysis.[12] Therefore, the major isomers of **4**−**7** were determined to be *N*-acyl form **A**. The minor isomers were considered to be *S*-acyl form **B**. In the ^{13}C NMR spectrum of **4**, two characteristic peaks for the minor isomer appeared at δ 158.8 and 201.2 in $CDCl_3$. The signal at δ 158.8 was assigned to the S−C=N carbon by comparison with related compounds 2-benzyloxycarbonylthio-5-methyl-1,3,4-thiadiazole (δ 157.3)[16] and 2-benzylthio-Δ^2-1,3-thiazoline (δ 164.3),[17] and the other signal at δ 201.2 was assigned to the thioester carbonyl carbon.[18]

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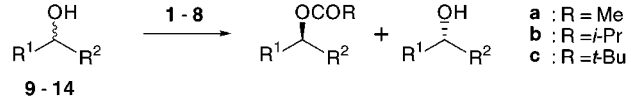
Table 2. Enantioselective Acylation of Racemic *sec*-Alcohols 9−14 with Twisted Amides 1−8

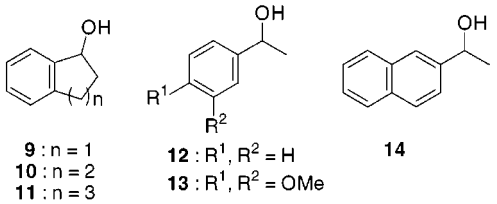


entry	alcohol[a]	amide	solv	additives[b]	*T*, °C	time, h	product	yield[c], %	ee, %	confign
1	**9**	**1**	hexane		reflux	114	**9a**	79	34	*S*
2	**9**	**2**	hexane		reflux	39	**9b**	84	39	*S*
3	**9**	**3**	hexane		reflux	22	**9c**	92	49	*S*
4	**9**	**3**	toluene		80	22	**9c**	97	37	*S*
5	**9**	**3**	CH_3COOEt		reflux	23	**9c**	94	36	*S*
6	**9**	**3**	$CHCl_3$		reflux	15	**9c**	89	35	*S*
7	**9**	**3**	*t*-BuOH		reflux	19	**9c**	70	33	*S*
8	**9**	**3**	THF		reflux	71	**9c**	72	26	*S*
9	**10**	**3**	hexane		reflux	18	**10c**	92	80	*S*
10	**10**	**4**	hexane		reflux	14	**10c**	99	57	*S*
11	**10**	**5**	hexane		reflux	15	**10c**	98	38	*S*
12	**10**	**6**	hexane		reflux	15	**10c**	97	44	*S*
13	**10**	**7**	hexane		reflux	14	**10c**	91	75	*S*
14	**10**	**8**	hexane		reflux	18	**10c**	51	16	*R*
15	**10**[d]	**3**	hexane		reflux	14	**10c**	92	70	*S*
16	**10**	**3**	hexane	Et_3N	rt	14	**10c**	87	84	*S*
17	**10**	**7**	hexane	Et_3N	rt	6 days	**10c**	93	79	*S*
18	**10**	**2**	hexane		reflux	18	**10b**	92	64	*S*
19	**11**	**3**	hexane		reflux	14	**11c**	90	46	*S*
20	**12**	**3**	hexane		reflux	28	**12c**	94	45	*S*
21	**13**	**3**	hexane		reflux	18	**13c**	93	50	*S*
22	**14**	**3**	hexane		reflux	12	**14c**	98	56	*S*
23	**9**	**3**	CH_2Cl_2	MeMgBr	0	2	**9c**	49	19	*R*
24	**9**	**4**	CH_2Cl_2	MeMgBr	0	4	**9c**	74	39	*R*
25	**11**	**3**	CH_2Cl_2	$MgBr_2/Et_3N$	rt	18	**11c**	58	20	*R*
26	**12**	**3**	CH_2Cl_2	MeMgBr	0	6	**12c**	53	42	*R*

[a] Five equiv of alcohol was used unless otherwise noted. [b] Five equiv of the reagent was added. [c] Isolated yields based on acylating agents. [d] Two equiv of alcohol was used.

On the other hand, amide **3** shows very different IR and ^{13}C NMR spectra compared to the others. The IR spectrum exhibited strong absorption bands of 1739 and 1130 cm^{-1} for the carbonyl and thiocarbonyl groups in the solid state. In contrast, a strong thioester carbonyl absorption at 1700 cm^{-1} and no trace of C=S absorption were detected in $CHCl_3$ solution. In the ^{13}C NMR data of the amide **3**, thioester carbonyl and the S−C=N carbon were observed at δ 201.6 and 158.8, respectively, which are very close to those of the minor isomer of amide **4** described above. Therefore, amide **3** mainly exists in the *S*-acyl form **B** in solution and exists in the *N*-acyl form **A** in the solid state. This suggests that the amides **3**−**7** would be in equilibrium between **A** and **B**.[19] To the best of our knowledge, the N to S acyl migration of *N*-acylthioimides has not yet been reported, although S to N acyl migration has been observed in the *S*-acylisothiourea[20] and *S*-(2-benzoxazolyl)thioester.[21]

Table 2 shows the results of the kinetic resolution of racemic *sec*-alcohols **9**−**14** with the amides **1**−**8** under various reaction conditions. The enantiomeric excess of the resulting esters was determined by HPLC analysis using a chiral stationary phase[22] after hydrolysis into the starting alcohols. Determination of the absolute configuration was performed by comparison of the specific rotations of the hydrolyzed alcohols with those reported.[23]



Each acylation of 5 equiv of 1-indanol (**9**) with amides **1**−**3** was carried out in hexane at reflux temperature for 22−114 h under neutral conditions to give (*S*)-1-indanoyl esters as major products in good yields. As the size of the acyl group increased, both the reaction rate[5] and the stereoselectivity increased (Table 2, entries 1−3). These observations may be due to the magnitude of the C(O)−N twist angle; as the twist angle increases by steric repulsion, amide resonance is inhibited; as a result, the reactivity increased. Since the twist angle determines the relative geometry between the carbonyl and the thiocarbonyl groups, the magnitude of the twist angle may play an important role in the stereoselectivity. Among the various solvents employed, hexane was the most effective, whereas tetrahydrofuran was the least effective, indicating that a less polar solvent is preferable in this reaction (Table 2, entries 4−8). A similar solvent effect has also been observed in the kinetic resolution of racemic amines.[24]

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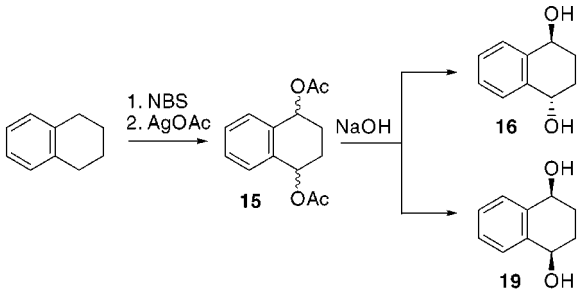
(20) (a) Pratt, R. F.; Bruice, T. C. *Biochemistry* **1971**, *10*, 3178. (b) Pratt, R. F.; Bruice, T. C. *J. Am. Chem. Soc.* **1972**, *94*, 2823.
(21) Ueda, M.; Seki, K.; Imai, Y. *Synthesis* **1981**, 991.
(22) The analysis was carried out using a CHIRALCEL OB column with a 9: 1 mixture of hexane and 2-propanol as an eluent solvent.
(23) Compd. **11**: Kabuto, K.; Imuta, M.; Kempner, E. S.; Ziffer, H. *J. Org. Chem.* **1978**, *43*, 2357. Compound **13**: Carter, M. B.; Schiott, B.; Gutierrez, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1994**, *116*, 11670. Compound **14**: Brunner, H.; Kurzinger, A. *J. Organomet. Chem.* **1988**, *346*, 413.

Scheme 2



The kinetic resolution of racemic 1-tetralol (**10**) with the amides **3**−**8** clearly shows the substituent effect at C-4. Depending on the substituent at C-4 of the thiazolidine-2-thione moiety, the selectivity was significantly changed (Table 2, entries 9−14); as the steric bulkiness of the substituent increased, the selectivity increased. Although amide **3** mainly exists in the *S*-acyl form in solution, the selectivity is 80% ee, which is the highest among the amides.

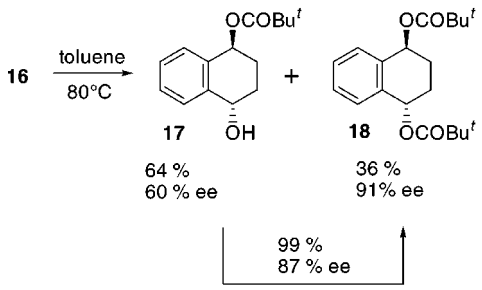
Although each reaction gave (*S*)-ester as the major product similar to the case of 1-indanol, only the reaction with the amide **8** gave an (*R*)-ester (Table 2, entry 14). Reducing the amount of 1-tetralol used from 5 to 2 equiv resulted in a slight decrease in the enantiomeric purity (Table 2, entry 15). Addition of triethylamine enhanced the reaction rate sufficiently to enable it to proceed even at room temperature and provided the highest enantioselectivity of 84% ee (Table 2, entries 16 and 17), although the reactivity of **7** was much lower than that of **3**.

This method was applicable to a variety of *sec*-alcohols. Each acylation of **11**−**14** with **3** gave (*S*)-esters as major products similar to the reactions described above. Comparing entry 19 with entries 3 and 9, the selectivity of **11** is close to that of **9**, but much different from that of **10** despite the closely related structures; therefore, the ring size exerts a significant effect on the stereoselectivity. Similar results were observed for isobutylation with **2** (Table 2, entries 2 and 18). On the other hand, the selectivities for acyclic alcohols **12**−**14** are similar, although their aromatic moieties are very different; therefore, the substituent on the aromatic part may not contribute to the enantioselectivity (Table 2, entries 20−22).

It is noteworthy that the addition of MeMgBr as a base or $MgBr_2$ as a Lewis acid reversed the stereoselectivity to yield the (*R*)-isomers predominantly (Table 2, entries 23−26). This observation is closely related to the reported kinetic resolution by Evans and his colleague[25] where asymmetric benzoylation of 1-tetralol with (*S*)-3-benzoyloxazolidinones in the presence of MeMgBr or $MgBr_2$ gave (*R*)-benzoate as a major product. The reversal of stereoselectivity may be ascribed to the change in the transition conformations around the amide bonds by chelation with the magnesium reagents.

This method is also applicable to the kinetic resolution of *dl*-diols. The racemic *dl*-diol **16** and *meso*-diol **19**[26] were prepared from tetralin via three steps (Scheme 2). Treatment of tetralin with NBS yielded a 1:1 mixture of *dl*- and *meso*-dibromides, which were converted into diacetates **15** with silver(I) acetate in 81% yield. After hydrolysis with 2 N NaOH, fractional recrystallization from the MeOH−ether afforded pure *dl*-diol **16** and *meso*-diol **19**.

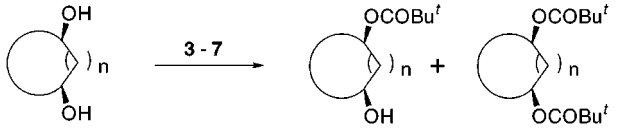
Scheme 3



The kinetic resolution of racemic *dl*-diol **16** with the amide **3** gave the corresponding monopivalate **17** and dipivalate **18** in 60% and 91% ee, respectively (Scheme 3). In this reaction, the ee of dipivalate **18** was higher than that of monopivalate **17**. This would be a result of the sequential enantioselective processes. In fact, the kinetic resolution of the isolated **17** afforded **18** with much higher ee as expected. A similar sequential process has been observed by Fu and co-workers.[4g]

Desymmetrization of *meso*-diols by way of a nonenzymatic acyl-transfer reaction has also been extensively explored for the preparation of chiral alcohols.[4] We applied the present asymmetric acylation method to the desymmetrization of *meso*-diols under very mild conditions. Desymmetrization of *meso*-1,2-, -1,3-, and -1,4-diols **19**−**22** with twisted amides **3**−**5** and **7** as acylating agents was investigated. The results are summarized in Table 3. Although 1,2- and 1,3-diols have often been employed as substrates for the nonenzymatic desymmet-

Table 3. Desymmetrization of *meso*-Diols 19−22 with Twisted Amides 3−7



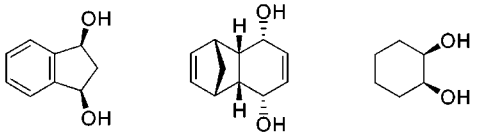
19 - 22 **19a - 22a** **19b - 22b**

entry	diol[a]	amide	additives	*T*, °C	time, h	monoester (**a**)/%	ee[b], %	diester (**b**), %
1	**19**	**4**		80	20	71[c]	71	27[c]
2	**19**	**5**		80	20	69[d] (52)[c]	48	21[d]
3	**19**	**3**		80	20	79[c]	79	17[c]
4	**19**	**7**		80	20	69[c]	78	28[c]
5	**19**	**3**	Et_3N (2 equiv)	rt	138	98[d] (34)[c]	88	0
6	**19**[e]	**3**	Et_3N (5 equiv)	rt	71	99[d] (41)[c]	82	0
7	**19**	**3**	DMAP (2 equiv)	rt	48	84[c]	51	0
8	**20**	**3**		80	14	78[c]	33	8[c]
9	**21**	**3**		80	14	92[d] (68)[c]	44	0
10	**2**[e]	**3**	Et_3N (2 equiv)	50	89	86[d] (37)[c]	56	0
11	**22**	**3**		80	15	86[d] (55)[c]	42[f]	0

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

(24) Nagao, Y.; Yagi, M.; Ikeda, T.; Fujita, E. *Tetrahedron Lett.* **1982**, *23*, 201.
(25) Evans, D. A.; Anderson, J. C.; Taylor, M. K. *Tetrahedron Lett.* **1993**, *34*, 5563.
(26) Martan, M.; Manassen, J.; Vofsi, D. *Tetrahedron* **1970**, *26*, 3815.

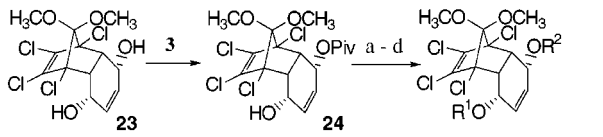
rization, there are few examples of using *sec-meso*-1,4-diols. The reactions of *cis*-tetrahydronaphthalene-1,4-diol (**19**) with 1.1 equiv of amides **3**−**5** and **7** in toluene at 80 °C for 20 h gave the corresponding monopivalate in good yields (Table 3, entries 1−4). Determination of the enantiomeric excess was performed by HPLC analysis using a chiral stationary phase. Among the amides, **3** and **7** are more effective for the stereoselective acylation than **4** and **5**. Addition of triethylamine enhances the reaction rate sufficiently to enable it to proceed even at room temperature with higher selectivity than that attained at 80 °C (Table 3, entries 5 and 6); however, amide **7** is less reactive than **3** at room temperature. Addition of DMAP decreases the enantioselectivity, although it very effectively accelerates the reaction rate (Table 3, entry 7). In the case of *cis*-1,3-indandiol (**20**), the selectivity was lower than that observed for 1,4-diol **19** (Table 3, entry 8), indicating the significant dependence of the structure of the diols on the stereoselectivity. The absolute configurations of the monoesters were determined by converting them into the corresponding known 1-tetralol and 1-indanol. Acylation of diol **21** with **3** at 80 °C gave the reported (*S*)-monopivalate[27] in 44% ee (Table 3, entry 9). Lowering the reaction temperature increased the selectivity to 56% ee (Table 3, entry 10). The chiral monoester of diol **21** and related compounds obtained by enzymatic desymmetrization have been proven to be useful building blocks for natural product synthesis.[28] In addition to the 1,3- and 1,4-diols, the present method was also applicable to a saturated 1,2-diol **22** (Table 3, entry 11).



20 **21** **22**

meso-1,4-Diol **23** has been used as the starting material for the synthesis of a macrolide antibiotic nodusmicin and its analogue 18-deoxynargenicin.[29] In the synthesis, it has been reported that attempts to generate the chiral monoacetate by esterification of **23** or hydrolysis of the diacetate of **23** with several enzymes failed.[29] These observations prompted us to study the desymmetrization of **23** by the present method. When diol **23** and 1.1 equiv of amide **3** in heptane were heated at reflux for 96 h, (*R*)-monoester **24a** was produced as a major isomer (61% ee) in 45% yield with diester **24b**. Determination of the absolute configuration was performed by converting **24a** to the reported monosilyl ether **28**[29] as described in Scheme 4, which is the intermediate for the synthesis of nodusmicin and 18-deoxynargenicin. After protection of the hydroxy group of **24a** with ethyl vinyl ether, hydrolysis of the pivalate gave a hydroxyether **26** in 78% yield. Protection of the resulting hydroxy group with *tert*-butyldimethylsilyl triflate and deprotection of the ethoxyethyl ether moiety yielded alcohol **28** (48%). The absolute configuration was in agreement with that reported in the literature.

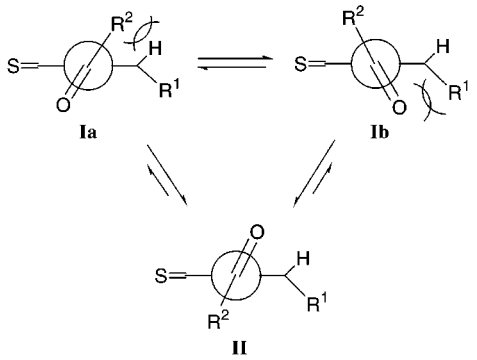
Scheme 4



23 **24**

25 R^1 = EE, R^2 = Piv
26 R^1 = EE, R^2 = H
27 R^1 = EE, R^2 = TBDMS
28 R^1 = H, R^2 = TBDMS

Scheme 5



Ia **Ib**

II

Table 4. Heats of Formations of the Rotamers of 1−8 and Their Twist Angles[a]

amide	ΔH_{fIa}, kcal mol^{-1}	ΔH_{fIb}, kcal mol^{-1}	ΔH_{fII}, kcal mol^{-1}	$\Delta\Delta H_f$, kcal mol^{-1}	τ, deg
3	−28.2	−29.0	−31.6	2.6	48.7
4	−28.8	−29.5	−30.8	1.3	47.3
5	−36.6	−37.6	−38.5	0.9	51.8
6	7.5	5.9	5.5	0.4	55.0
7	−65.6		−69.04	3.4	45.2
8			0.97		27.6

[a] Predicted by AM1 method.

To obtain mechanistic information, structural optimization of the amides **3**−**8** was performed by the AM1 method.[30] The calculations predicted three stable rotamers **Ia**, **Ib**, and **II** (Scheme 5). The number of rotamers depends on the structure of the amides: one rotamer for **8**, two rotamers for **7**, three rotamers for **3**−**6**. Rotamers **Ia** and **Ib** have the conformation where the R and R′ groups are on opposite sides of the thiazolidine-2-thione plane, whereas the R and R′ of rotamer **II** are on the same side. The ΔH_f, $\Delta\Delta H_f$, and twist angle τ are summarized in Table 4.

It is clear that rotamers **II** have lower energy than **Ia** or **Ib** in all cases, indicating the thermodynamic preference of rotamer **II**. The X-ray geometry of amide **5**[13] is almost in agreement with that of the corresponding rotamer **II**. The values of the twist angle τ,[31] which were determined on the basis of the rotamer **II**, show that the amide bond of **3**−**8** is extremely twisted. The twist angle of 65.5° of the amide **5** determined by X-ray analysis is almost in agreement with that of the predicted value of 51.8°, suggesting the validity of the results of the calculations. The $\Delta\Delta H_f$ values, which are the difference in the ΔH_f values between **I** and **II**, are influenced by the C-4 substituent. The order of magnitude of the $\Delta\Delta H_f$ is in agreement with that of the stereoselectivity. In fact, the stereoselectivities in the kinetic resolution of **10** and

(27) Takano, S.; Higashi, Y.; Kamikubo, T.; Moriya, M.; Ogasawara, K. *Synthesis* **1993**, 948.
(28) For example: (a) Takano, S.; Moriya, M.; Hayashi, Y.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1993**, 177. (b) Kamikubo, T; Hiroya, K.; Ogasawara, K. *Tetrahedron Lett.* **1996**, *37*, 499.
(29) Gössinger, E.; Graupe, M.; Kratky, C.; Zimmermann, K. *Tetrahedron* **1997**, *53*, 3083.
(30) AM1 calculations were performed by using CS MOPAC Pro with MMOK empirical amide correction factor.
(31) Winkler, F. K.; Dunitz, J. D. *J. Mol. Biol.* **1971**, *59*, 169.

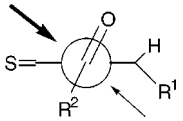


Figure 3. Nucleophilic attack from less hindered side.

desymmetrization of **19** with amides **3-7** increased with increasing $\Delta\Delta H_f$ (entries 9−13 in Tables 2 and entries 1−4 in Table 3).

Although the mechanism for the generation of the stereoselectivity in this reaction is still unclear, the experimental results described above suggest that the conformation of the twisted amide plays an important role. Thus, since rotamers **I** and **II** have opposite axial chirality, the rotamer ratio would exert a significant effect on the stereoselectivity in this reaction. In fact, the relationships between the $\Delta\Delta H_f$ and the stereoselectivity were observed in the kinetic resolution of **10** and desymmetrization of **19** with amides **3**−**7**. This observation strongly suggests that the reaction proceeds from the rotamer **II**.[32] Since nucleophiles attack the amide carbonyl from the less hindered side, they will approach from the side of the thiocarbonyl group as shown in Figure 3. Although this working model cannot be applied directly to amide **3** that mainly exists as the *S*-acyl form in solution, one possible explanation may be given as follows: if the reactivity of the *N*-acyl form is significantly higher than that of the *S*-acyl form and the rate of the S to N acyl migration is faster than that of the acylation, the reaction proceeds from the *N*-acyl form according to the above working model.

In contrast to the reaction with amides **3**−**7**, that of amide **8** resulted in a reversal of stereoselectivity despite the conformational preference of rotamer **II**. This can be ascribed to the difference in the substituent at C-4. Thus, since the 3-methyl-3*H*-imidazol-4-yl group of **8** can effect hydrogen bonding with an alcohol, the alcohol would approach from the side of the imidazolyl group and attack the amide carbonyl as shown in Figure 3. This difference in the direction of attack by the alcohol may cause the reversal of the stereoselectivity.

The role of the asymmetric center at the 4-position is to control the directionality of the amide bond twisting and to induce axial chirality, which would enable discrimination of the two hydroxy groups of racemic *sec*-alcohols and *meso*-diols. Similar induced axial chirality has been postulated in the diastereoselective Diels−Alder reaction of 2-(*β*-substituted α,*β*-unsaturated)acyl-3-phenyl-l-menthopyrazoles.[33] In the latter reaction, the directionality of the phenyl group rotation is controlled by the adjacent chiral center, which causes the face-selectivity in the Diels−Alder reaction.

In summary, these asymmetric acylations were attained by taking advantage of the following two important characteristic features of the twisted amides: (1) high reactivity of the amide carbonyl due to inhibition of amide resonance, which enables the acylation reaction under neutral and mild conditions, and (2) axial chirality induced by the adjacent chiral center, which enables discrimination of the two enantiomeric hydroxy groups. It is interesting to note that an axially chiral twisted amide is postulated to be a transition-state intermediate of a peptide substrate during enzymatic hydrolysis.[34]

Experimental Section

Melting points are uncorrected. Column chromatography was carried out using Merck silica gel 60, Merck silica gel 60 PF_{254}, or Florisil (100−200 mesh). HPLC was carried out using a Daicel CHIRALPAK OB column (25 cm × 4.6 mm) or AS column (25 cm × 4.6 mm). IR spectra were obtained as neat films between NaCl plates, as KBr pellets, or as a $CHCl_3$ solution using a NaCl chamber. ^{1}H NMR spectra were recorded at 270 or 400 MHz as dilute solutions in $CDCl_3$, CD_3OD, C_6D_6, or $C_6D_5CD_3$, and the chemical shifts were reported relative to internal TMS. ^{13}C NMR spectra were recorded at 67.9 or 100.4 MHz as dilute solutions in $CDCl_3$, and the chemical shifts were reported relative to internal TMS. High- and low-resolution mass spectra were recorded at an ionizing voltage of 70 eV by electron impact.

Preparation of (4*S*)-4-*tert*-Butyl-1,3-thiazolidine-2-thione and (4*S*)-4-*tert*-Butyl-1,3-oxazolidine-2-thione.[7] Concentrated sulfuric acid (2.6 mL) was added dropwise to a round-bottom flask containing L-*tert*-leucinol (2.14 g, 15.2 mmol), which was derived from L-*tert*-leucine[35] at 0 °C, and the mixture was vigorously stirred for 1.5 h. Then, potassium *O*-ethyl dithiocarbonate (3.67 g, 22.9 mmol), 2 M NaOH (34 mL), and water (15 mL) were added to the reaction mixture, and the solution was heated at 50 °C for 2 h. Potassium *O*-ethyl dithiocarbonate (3.67 g, 22.9 mmol) and 2 M NaOH (4 mL) were again added to the reaction mixture, and the solution was heated at 50 °C further 15.5 h. After being cooled to room temperature, the solution was acidified with 2 M HCl and extracted with $CHCl_3$ (35 mL × 3). The combined extracts were washed with water and dried over anhydrous $MgSO_4$. Evaporation of the solvent gave a crude mixture of products, which was subjected to column chromatography (silica gel) using 5:2−1:0 mixture of $CHCl_3$ and hexane as eluent solvents to give two crystalline compounds. The less polar fraction was (4*S*)-4-*tert*-butyl-1,3-thiazolidine-2-thione (1.44 g, 54% from L-*tert*-leucine) The spectroscopic data was in agreement with those reported:[7] mp 143−144 °C; $[\alpha]^{27}_D = -33.2°$ (*c* 1.03, $CHCl_3$). The polar fraction was (4*S*)-4-*tert*-butyl-1,3-oxazolidine-2-thione (0.166 g, 7% from L-*tert*-leucine): mp 153−156 °C; $[\alpha]^{27}_D = -11.8°$ (*c* 0.982, $CHCl_3$).

Preparation of (4*S*)-4-*tert*-Butyl-3-isobutyryl-1,3-thiazolidine-2-thione (2). To a solution of (4*S*)-4-*tert*-butyl-1,3-thiazolidine-2-thione (300 mg, 1.71 mmol) and triethylamine (600 *μ*L, 4.30 mmol) in dry CH_2Cl_2 (6 mL) was added dropwise isobutyryl chloride (270 *μ*L, 2.58 mmol) at 0 °C, and the solution was stirred at room temperature for 1 h. The reaction mixture was washed with water, dried over anhydrous $MgSO_4$, and concentrated to give a crude product. This was subjected to column chromatography (Florisil) using a 2:1 mixture of hexane and $CHCl_3$ as an eluent solvent to give amide **2** (421 mg, 100%). Recrystallization from hexane gave analytical specimen of **2**: mp 69.0−71.0 °C; $[\alpha]^{28}_D = +595°$ (*c* 1.11, $CHCl_3$); IR (KBr) 2963, 1691, 1250, 1133 cm$^{-1;}$ IR ($CHCl_3$) 1696 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 1.03 (s, 9H), 1.15 (d, *J* = 6.7 Hz, 3H), 1.28 (d, *J* = 6.7 Hz, 3H), 3.09 (d, *J* = 12.0 Hz, 1H), 3.52 (dd, *J* = 8.2, 12.0 Hz, 1H), 4.52 (sept, *J* = 6.7 Hz, 1H), 5.38 (d, *J* = 8.2 Hz, 1H); ^{13}C NMR (100.4 MHz, $CDCl_3$) *δ* 18.9, 20.8, 26.9, 30.3, 33.0, 38.0, 72.5, 177.9, 204.6; MS *m*/*z* 245 (M^+, 77), 146 (100), 118 (45), 71 (47); HRMS calcd for $C_{11}H_{19}NOS_2$ 245.0908, found 245.0906.

Preparation of (4*S*)-4-*tert*-Butyl-3-pivaloyl-1,3-thiazolidine-2-thione (3). To a solution of (4*S*)-4-*tert*-butyl-1,3-thiazolidine-2-thione (781 mg, 4.46 mmol) and triethylamine (4.35 *μ*L, 11.2 mmol) in dry CH_2Cl_2 (16 mL) was added dropwise pivaloyl chloride (825 *μ*L, 6.7 mmol) at 0 °C, and the

(32) This hypothesis is more valid than our previous one, which assumed rotamer **I** was the major isomer (ref 10a).

(33) Kashima, C.; Fukusaka, K.; Takahashi, K.; Yokoyama, Y. *J. Org. Chem*. **1999**, *64*, 1108.

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(35) McKennon, M. J.; Meyers, A. I. *J. Org. Chem*. **1993**, *58*, 3568.

solution was stirred at room temperature for 2 h. The reaction mixture was washed with water, dried over anhydrous $MgSO_4$, and concentrated to give a crude product, which was recrystallized from hexane to yield a pure amide **3** (984 mg, 85%): mp 78.5−79.5 °C; $[\alpha]^{28}_D = -85.6°$ (*c* 1.02, $CHCl_3$); IR (KBr) 1739, 1387, 1249. 1130, 1004 cm^{-1}; IR ($CHCl_3$) 1700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.01 (s, 9H), 1.28 (s, 9H), 3.17 (t, $J = 10.8$ Hz, 1H), 3.28 (dd, $J = 9.0$, 10.8 Hz, 1H), 4.15 (dd, $J = 9.0$, 10.8 Hz, 1H); ^{13}C NMR (100.4 MHz, $CDCl_3$) δ 26.7, 27.1, 34.4, 35.0, 47.6, 86.1, 158.8, 201.6; MS *m*/*z* 259 (M^+, 2), 118 (16), 85 (14), 57 (100); HRMS calcd for $C_{12}H_{21}NOS_2$ 259.1064, found 259.1057.

Preparation of (4*S*)-4-Isopropyl-3-pivaloyl-1,3-thiazolidine-2-thione (4). To a solution of (4*S*)-4-isopropyl-1,3-thiazolidine-2-thione (1.00 g, 6.21 mmol) and triethylamine (1.73 mL, 12.4 mmol) in dry CH_2Cl_2 (50 mL) was added dropwise pivaloyl chloride (0.92 mL, 7.45 mmol) at 0 °C, and the solution was stirred at room temperature for 24 h. The reaction mixture was washed with water, dried over anhydrous $MgSO_4$, and concentrated to give a crystalline product, which was recrystallized from hexanes−ether to afforded a pure **4** (1.42 mg, 93%): mp 117.5−119.5 °C; $[\alpha]^{28}_D = -27.1°$ (*c* 1.02, $CHCl_3$); IR (KBr) 2970, 1735, 1414, 1125 cm^{-1}; IR ($CHCl_3$) 1726 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.98 (d, $J = 6.8$ Hz, 0.6H), 0.98 (d, $J = 6.8$ Hz, 2.4H), 1.06 (d, $J = 6.8$ Hz, 0.6H), 1.07 (d, $J = 6.8$ Hz, 2.4H), 1.28 (s, 0.2H), 1.41 (s, 0.8H), 2.02−2.13 (m, 1H), 3.11 (dd, $J = 10.3$, 11.2 Hz, 0.2H), 3.35 (dd, $J = 9.3$, 11.2 Hz, 0.2H), 3.40 (d, $J = 9.8$ Hz, 1.6H), 4.24 (td, $J = 6.3$, 9.8 Hz, 0.2H), 4.55 (td, $J = 3.4$, 8.3 Hz, 0.8H); ^{13}C NMR (67.8 MHz, $CDCl_3$, major isomer) δ 15.4, 19.1, 27.9, 29.7, 30.9, 44.5, 74.1, 188.0, 200.4; ^{13}C NMR (67.8 MHz, $CDCl_3$, minor isomer) δ 18.8, 19.5, 27.0, 32.8, 35.7, 47.6, 82.1, 158.8, 201.2; MS *m*/*z* 245 (M^+, 18), 118 (4), 85 (10), 55 (100); HRMS calcd for $C_{11}H_{19}NOS_2$ 245.0908, found 245.0893.

Preparation of (4*S*)-4-isobutyl-3-pivaloyl-1,3-thiazolidine-2-thione (5):[12] mp 89.0−91.0 °C (lit.[13] mp 88.5−91.5 °C); $[\alpha]^{28}_D = -0.971°$ (*c* 1.03, $CHCl_3$).

Preparation of (4*S*)-4-Benzyl-3-pivaloyl-1,3-thiazolidine-2-thione (6). To a solution of (4*S*)-4-benzyl-1,3-thiazolidine-2-thione (1.00 g, 4.80 mmol) and triethylamine (0.8 mL, 5.7 mmol) in dry CH_2Cl_2 (50 mL) was added dropwise pivaloyl chloride (0.71 mL, 5.7 mmol) at 0 °C, and the solution was stirred at room temperature for 19 h. The reaction mixture was washed with water, dried over anhydrous $MgSO_4$, and concentrated to give a crystalline product, which was recrystallized from hexanes−ether to yield pure **6** (1.26 mg, 89%): mp 119−121 °C; $[\alpha]^{28}_D = -6.31°$ (*c* 1.07, $CHCl_3$); IR (KBr) 2979, 1721, 1264, 1169, 1011 cm^{-1}; IR ($CHCl_3$) 1727 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.46 (s, 9H), 2.88 (dd, $J = 11.0$, 12.9 Hz, 1H), 3.21−3.32 (m, 3H), 4.65 (quint, $J = 3.7$ Hz, 1H), 7.18−7.35 (m, 5H); ^{13}C NMR (100.4 MHz, $CDCl_3$) δ 27.97, 28.03, 28.06, 36.3, 38.4, 44.6, 70.3, 127.4, 128.99, 129.03, 135.5, 188.6, 200.1; MS *m*/*z* 293 (M^+, 12), 202 (17), 118 (31), 85 (14), 55 (100); HRMS calcd for $C_{15}H_{19}NOS_2$ 293.0959, found 293.0934.

Preparation of (4*S*)-4-*tert*-Butyl-3-pivaloyl-1,3-oxazolidine-2-thione (7). To a solution of (4*S*)-4-*tert*-butyl-1,3-oxazolidine-2-thione (1.00 g, 6.30 mmol) and triethylamine (1.75 mL, 12.6 mmol) in dry CH_2Cl_2 (20 mL) was added dropwise pivaloyl chloride (930 μL, 7.55 mmol) at 0 °C, and the solution was stirred at room temperature for 4 h. The reaction mixture was washed with water, dried over anhydrous $MgSO_4$, and concentrated to yield a crystalline product, which was washed with hexane to give pure amide **7** (1.44 g, 94%). Recrystallization from hexane−CH_2Cl_2 gave an analytical specimen of **7**: mp 176−178 °C; $[\alpha]^{28}_D = -43.7°$ (*c* 1.09, $CHCl_3$); IR (KBr) 1734, 1374, 1286, 1205, 920 cm^{-1}; IR ($CHCl_3$) 1730 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.95 (s, 9H), 1.53 (s, 9H), 4.46 (dd, $J = 2.4$, 4.9 Hz, 1H), 4.49−4.53 (m, 2H); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 25.7, 28.7, 35.0, 44.6, 69.4, 70.1, 184.8, 187.6; MS *m*/*z* 243 (M^+, 43), 186 (36), 158 (11), 85 (58), 57 (100); HRMS calcd for $C_{12}H_{21}NO_2S$ 243.1293, found 243.1298.

Preparation of (4*S*)-4-[(3-Methyl-3*H*-imidazol-4-yl)-methyl]-1,3-oxazolidine-2-thione. To a solution of N^{π}-methyl-L-histidinol dihydrochloride[13] (1.79 g, 7.85 mmol) in EtOH (35 mL) and 0.9 M KOH (35 mL) was added dropwise carbon disulfide (906 μL, 14.9 mmol), and the solution was stirred at 80 °C for 4 h. After being cooled to room temperature, the solution was neutralized with 2 M HCl. Evaporation of the solvent gave a crude product, which was subjected to column chromatography (silica gel) using a 4:1 mixture of $CHCl_3$ and MeOH as an eluent solvent to yield (4*S*)-4-[(3-Methyl-3*H*-imidazol-4-yl)methyl]-1,3-oxazolidine-2-thione (945 mg, 61%). Recrystallization from MeOH−ether afforded an analytical specimen: mp 181−183 °C; $[\alpha]^{27}_D = -17.3°$ (*c* 0.968, MeOH); IR (KBr) 3129, 1550, 1509, 1288, 1181 cm^{-1}; ^1H NMR (270 MHz, CD_3OD) δ 2.83 (d, $J = 5.9$ Hz, 2H), 3.56 (s, 3H), 4.22−4.34 (m, 1H), 4.28 (dd, $J = 8.6$, 11.7 Hz, 1H), 4.62 (t, $J = 8.6$ Hz, 1H), 6.76 (s, 1H), 7.51 (s, 1H); MS *m*/*z* 197 (M^+, 5), 96 (100); HRMS calcd for $C_8H_{11}N_3OS$ 197.0623, found 197.0641.

Preparation of (4*S*)-4-[(3-Methyl-3*H*-imidazol-4-yl)-methyl]-3-pivaloyl-1,3-oxazolidine-2-thione (8). To a solution of (4*S*)-4-[(3-methyl-3*H*-imidazol-4-yl)methyl]-1,3-oxazolidine-2-thione (50.3 mg, 0.255 mmol) and triethylamine (160 μL, 1.15 mmol) in dry CH_2Cl_2 (2.5 mL) was added dropwise pivaloyl chloride (48 μL, 0.39 mmol) at 0 °C, and the solution was stirred at room temperature for 2.5 h. The reaction mixture was washed with water, dried over anhydrous $MgSO_4$, and concentrated to give a crude product. This was subjected to column chromatography (Florisil) using a 10:1 mixture of $CHCl_3$ and MeOH as an eluent solvent to give amide **8** (51.6 mg, 72%): $[\alpha]^{22}_D = +59.2°$ (*c* 1.05, CH_2Cl_2); IR (neat) 2973, 1734, 1507, 1481, 1395, 1367, 1283, 1194 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.50 (s, 9H), 2.86 (dd, $J = 10.7$, 14.9 Hz, 1H), 3.13 (dd, $J = 3.4$, 14.9 Hz, 1H), 3.63 (s, 3H), 4.34 (dd, $J = 5.8$, 9.1 Hz, 1H), 4.52 (dd, $J = 7.6$, 9.1 Hz, 1H), 4.60−4.66 (m, 1H), 6.84 (s, 1H), 7.45 (s, 1H); ^{13}C NMR (100.4 MHz, $CDCl_3$) δ 26.6, 28.0, 31.5, 44.1, 60.7, 72.1, 125.4, 128.1, 139.0, 184.2, 186.2; MS *m*/*z* 281 (M^+, 55), 57 (100); HRMS calcd for $C_{13}H_{19}N_3O_2S$ 281.1198, found 281.1219.

General Procedure for the Kinetic Resolution of Racemic *sec*-Alcohols with Twisted Amides 1−8. A mixture of an amide (0.18 mmol) and 5 equiv of an alcohol in an appropriate solvent (3 mL) was heated under reflux for 15−138 h. The reaction mixture was concentrated and separated by preparative TLC using a 5:1 mixture of hexane and ethyl acetate as an eluent solvent to yield esters. After hydrolysis of the esters with 2 M NaOH, the enantiomeric excess of the product was determined by HPLC analysis using a Daicel CHIRALPAK OB column with a 10:1 mixture of hexane and *i*-PrOH as an eluent solvent.

1-Indanoyl pivalate (9c): IR (neat) 3032, 2971, 1726, 1282, 1149 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.20 (s, 9H), 1.98−2.06 (m, 1H), 2.50−2.58 (m, 1H), 2.88 (ddd, $J = 6.1$, 8.5, 16.0 Hz, 1H), 3.09 (ddd, $J = 5.4$, 8.8, 16.0 Hz, 1H), 6.18 (dd, $J = 4.6$, 7.1 Hz, 1H), 7.20−7.35 (m, 4H); MS *m*/*z* 218 (M^+, 0.2), 117 ([M − $OCOBu^t$]$^+$, 100), 55 (39); HRMS calcd for C_9H_9 ([M − $OCOBu^t$]]$^+$) 117.0704, found 117.0676.

1-Tetraloyl isobutylate (10b): IR (neat) 2939, 1733, 1191, 1151, 765 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.16 (d, $J = 2.0$ Hz, 3H), 1.19 (d, $J = 2.0$ Hz, 3H), 1.78−2.02 (m, 4H), 2.55 (sept., $J = 6.9$ Hz, 1H), 2.70−2.92 (m, 2H), 5.98 (t, $J = 4.6$ Hz, 1H), 7.10−7.25 (m, 4H); MS *m*/*z* 218 (M^+, 4), 148 (35), 131 (91), 130 (100), 115 (21), 91 (22), 43 (9); HRMS calcd for $C_{14}H_{18}O_2$ 218.1307, found 218.1299.

1-Tetraloyl pivalate (10c): IR (neat) 3032, 2936, 1724, 1281, 1148 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.20 (s, 9H), 1.80−2.04 (m, 4H), 2.73−2.90 (m, 2H), 5.95 (d, $J = 4.6$ Hz, 1H), 7.11−7.26 (m, 4H); MS *m*/*z* 232 (M^+, 9), 148 (6), 131 (100), 115 (2), 91 (4), 55 (16); HRMS calcd for $C_{15}H_{20}O_2$ 232.1464, found 232.1420.

5-Pivaloyloxy-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-one (11c): IR (neat) 2931, 1729, 1480, 1456, 1369, 1157, 1033, 759 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.26 (s, 9H), 1.59−1.80 (m, 2H), 1.83−2.03 (m, 4H), 2.76 (m, 1H), 2.99 (dd, $J = 10.9$, 14.2 Hz, 1H), 5.91 (d, $J = 7.9$ Hz, 1H), 7.14 (m, 3H), 7.31 (m, 1H); MS *m*/*z* 246 (M^+, 3), 162 (2), 145 (59), 144 (49), 57 (13), 28 (100); HRMS calcd for $C_{16}H_{22}O_2$ 246.1620, found 246.1587.

1-Phenyl-1-ethanoyl pivalate (12c): IR (neat) 3032, 2978, 1730, 1281, 1158, 1063 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$)

δ 1.20 (s, 9H), 1.51 (d, J = 6.6 Hz, 3H), 5.85 (q, J = 6.6 Hz, 1H), 7.30−7.39 (m, 5H); MS m/z 206 (M^+, 26), 122 (3), 105 (100), 55 (45); HRMS calcd for $C_{13}H_{18}O_2$ 206.1307, found 206.1305.

1-(3,4-Dimethoxyphenyl)-1-ethanoyl pivalate (13c): IR (neat) 2977, 1726, 1595, 1520, 1463, 1264, 1030, 809 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.20 (s, 9H), 1.51 (d, J = 6.6 Hz, 3H), 3.87 (s, 3H), 3.88 (s, 3H), 5.80 (q, J = 6.6 Hz, 1H), 6.78−6.92 (m, 3H); MS m/z 266 (M^+, 94), 182 (7), 165 (100), 57 (24); HRMS calcd for $C_{15}H_{22}O_4$ 266.1518, found 266.1472.

1-(2-Naphthyl)-1-ethanoyl pivalate (14c): mp 72.5−73.4 °C; IR (KBr) 2960, 1715, 1603, 1508, 1159, 1047, 825, 753 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.23 (s, 9H), 1.60 (d, J = 6.6 Hz, 3H), 6.01 (q, J = 6.6 Hz, 1H), 7.47 (m, 3H), 7.81 (m, 4H); MS m/z 256 (M^+, 5), 172 (3), 155 (18), 57 (6), 28 (100); HRMS calcd for $C_{17}H_{20}O_2$ 256.1463, found 256.1447.

Synthesis of a Mixture of *meso*- and *dl*-1,2,3,4-Tetrahydronaphthalene-1,4-diacetate (15). A solution of tetralin (5.00 g, 37.9 mmol), NBS (14.8 g, 75.8 mmol), and AIBN (186 mg, 1.13 mmol) in CCl_4 (50 mL) was refluxed for 20 min. After the solution was cooled to room temperature, an insoluble material was filtered off and the filtrate was concentrated to give a crude dibromide. To a solution of the dibromide in acetic acid (40 mL) and dry DMF (12 mL) was added silver(I) acetate (12.6 g, 75.7 mmol) at 0 °C, and the solution was stirred at room temperature for 2 h. The resulting precipitate of silver bromide was filtered off, and the filtrate was concentrated. After the residue was neutralized with saturated $NaHCO_3$, the solution was extracted three times with ethyl acetate. The combined organic layer was washed twice with 5% $Na_2S_2O_3$ and dried over anhydrous $MgSO_4$. Concentration of the solution to give a crystalline product, which was washed with hexane to give a 1:1.75 mixture of *dl*- and *meso*-**15** (7.62 g): ^1H NMR (400 MHz, $CDCl_3$) for *dl*-**15** δ 1.95−1.99 (m, 2H), 2.07 (s, 6H), 2.27−2.30 (m, 2H), 6.05 (t, J = 2.1 Hz, 2H), 7.34 (br s, 4H); ^1H NMR (400 MHz, $CDCl_3$) for *meso*-**15** δ 2.09−2.12 (m, 4H), 2.13 (s, 6H), 5.96 (m, 2H), 7.32 (br s, 4H); MS m/z 188 ([M − CH_3-COOH]$^+$, 11), 148 (100); HRMS calcd for $C_{12}H_{12}O_2$ ([M − CH_3-COOH]$^+$) 188.0838, found 188.0832.

Synthesis of *dl*-1,2,3,4-Tetrahydronaphthalene-1,4-diol (16) and *meso*-1,2,3,4-Tetrahydronaphthalene-1,4-diol (19).[23] To a solution of 1:1 mixture of *dl*- and ***meso*-15** (1.36 g, 5.48 mmol) in MeOH (30 mL) was added 2 M NaOH (7 mL), and the solution was stirred at room temperature for 2 h. Then the solution was acidified with 2 M HCl and concentrated in vacuo. The residue was dissolved in EtOH−$CHCl_3$, and the insoluble inorganic salt was filtered off. The filtrate was concentrated to give a mixture of **16** and **19**, which was separated by fractional crystallization using MeOH−ether to yield pure **16** and **19**.[26] *dl*-Diol **16**: mp 141−142 °C; IR (KBr) 3278, 2866, 1507, 1050, 761 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.83 (m, 2H), 2.31 (dt, J = 2.5, 11.0 Hz, 2H), 4.84 (br s, 2H), 7.33 (m, 2H), 7.46 (m, 2H); MS m/z 164 (M^+, 0.6), 146 ([M − H_2O]$^+$ 100), 145 (98), 131 (72), 128 (20); HRMS calcd for $C_{10}H_{12}O$ ([M − H_2O]$^+$) 146.0731, found 146.0686.

General Procedure for the Kinetic Resolution of 16 with Twisted Amide 3. A mixture of **3** and **16** in appropriate solvent (3 mL) was stirred at 80 °C to refluxing temperature for 18−20 h. The reaction mixture was concentrated and separated by preparative TLC using a 10:1 mixture of $CHCl_3$ and ethyl acetate as an eluent solvent to yield *trans*-1,2,3,4-tetrahydro-1-pivaloyloxy-4-naphthol **(17)** and *trans*-1,2,3,4-tetrahydronaphthalene-1,4-dipivalate **(18)**. Analytical crystalline **17** was obtained by recrystallization from hexane: mp 55.0−57.0 °C; IR (KBr) 3264, 2971, 1719, 1156, 765 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.20 (s, 9H), 1.83−1.93 (m, 2H), 2.20−2.39 (m, 2H), 4.88 (br s, 1H), 5.98 (t, J = 4.8 Hz, 1H), 7.26 (d, J = 7.6 Hz, 1H), 7.30 (td, J = 1.5, 7.6 Hz, 1H), 7.36 (td, J = 1.5, 7.6 Hz, 1H), 7.48 (d, J = 7.6 Hz, 1H); MS m/z 248 (M^+, 0.1), 230 ([M − H_2O]$^+$, 8), 131(100); HRMS calcd for $C_{15}H_{18}O_2$ ([M − H_2O]$^+$) 230.1307, found 230.1338. The enantiomeric excess of **18** was determined by HPLC analysis using a Daicel CHIRALPAK AS column with a 10:1 mixture of hexane and *i*-PrOH as an eluent solvent. Recrystallization from hexane gave analytical specimen of **18**: mp 58.0−59.5 °C; IR (KBr) 2958, 1730, 1154, 1119, 753 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.20 (s, 18H), 1.90 (dd, J = 2.4, 3.5 Hz, 1H), 1.93 (dd, J = 1.2, 3.5 Hz, 1H), 2.26 (dd, J = 1.2, 2.4 Hz, 1H), 2.29 (t, J = 2.4 Hz, 1H), 6.02 (t, J = 2.4 Hz, 2H), 7.28−7.33 (m, 4H); MS m/z 231 ([M − OCOBu^t]$^+$, 6), 230 ([M − t-BuCOOH]$^+$, 34), 146 (50), 129 (100), 57 (30); HRMS calcd for $C_{15}H_{18}O_2$ ([M − t-BuCOOH]$^+$) 230.1307, found 230.1338. After hydrolysis of **18** into corresponding diol **16** with 2 mol dm^{-3} NaOH, the enantiomeric excess was determined by HPLC analysis using a Daicel CHIRALPAK OB column with a 4:1 mixture of hexane and *i*-PrOH as an eluent solvent.

Kinetic Resolution of 17 with Twisted Amide 3. A mixture of **3** and **17** in dry toluene (1 mL) was stirred at 80 °C for 16−17 h. The reaction mixture was concentrated and separated by preparative TLC using a 5:1 mixture of hexane and ethyl acetate as an eluent solvent to yield **18.** After hydrolysis of **18**, the enantiomeric excess of the corresponding diol was determined in a similar manner as described above.

General Procedure for the Desymmetrization of *meso*-Diols with Twisted Amides 3−5 and 7. A mixture of a *meso*-diol (0.2 mmol), 1.1 equiv of an amide, and additives in appropriate solvent (3 mL) was stirred at room temperature to refluxing temperature for 14−138 h. The reaction mixture was concentrated and separated by preparative TLC to yield monoesters and diesters.

***cis*-1,2,3,4-Tetrahydro-1-pivaloyloxy-4-naphthol (19a).** The enantiomeric excess was determined by HPLC analysis using a Daicel CHIRALPAC AS column with a 10:1 mixture of hexane and *i*-PrOH as an eluent solvent: IR (neat) 3420, 1736, 1284, 1161, 1150, 1042, 773, 734 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.21 (s, 9H), 1.99−2.11 (m, 4H), 4.75 (dd, J = 3.7, 4.6 Hz, 1H), 5.89 (br s, 1H), 7.23 (d, J = 7.6 Hz, 1H), 7.28 (td, J = 1.5, 7.6 Hz, 1H), 7.34 (td, J = 1.5, 7.4 Hz, 1H), 7.34 (d, J = 7.6 Hz, 1H); MS m/z 248 (M^+, 0.1), 230 ([M − H_2O]$^+$, 26), 146 (32), 129 (51), 57 (18), 28 (100); HRMS calcd for $C_{15}H_{18}O_2$ ([M − H_2O]$^+$) 230.1307, found 230.1335.

***cis*-1,4-Dipivaloyloxy-1,2,3,4-tetrahydronaphthalene (19b).** Recrystallization from hexane gave analytical specimen of **19b**: mp 67.0−68.5 °C; IR (KBr) 1725, 1281, 1155, 764 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.24 (s, 18H), 2.00−2.16 (m, 4H), 5.91 (t, J = 5.6 Hz, 2H), 7.25−7.32 (m, 4H); MS m/z 231 ([M − OCO-t-Bu]$^+$, 2), 230 ([M − t-BuCCOOH]$^+$, 14), 146 (20), 129 (41), 57 (13), 28 (100); HRMS calcd for $C_{15}H_{18}O_2$ ([M − t-BuCCOOH]$^+$) 230.1307, found 230.1337.

***cis*-1-Pivaloyloxy-3-indanol (20a):** IR (neat) 2971, 1727, 1158, 757 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.22 (s, 9H), 1.93 (dt, J = 5.4, 14.1 Hz, 1H), 3.03 (dt, J = 6.8, 14.1 Hz, 1H), 5.13 (m, 1H), 6.01 (dd, J = 5.4, 6.8 Hz, 1H), 7.34−7.43 (m, 3H), 7.49 (d, J = 7.3 Hz, 1H); MS m/z 216 ([M − H_2O]$^+$, 11), 133 (47), 115 (26), 57 (46), 28 (100); HRMS calcd for $C_{14}H_{16}O_2$ ([M − H_2O]$^+$) 216.1150, found 216.1135.

***cis*-1,3-Dipivaloyloxyindane (20b):** IR (neat) 2974, 1730, 1147 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.22 (s, 18H), 1.98 (dt, J = 4.6, 14.4 Hz, 1H), 3.06 (dt, J = 7.1, 14.4 Hz, 1H), 6.09 (dd, J = 4.6, 7.1 Hz, 2H), 7.39 (s, 4H); MS m/z 216 ([M − t-BuCCOOH]$^+$, 31), 132 (29), 115 (100), 85 (20), 57 (40), 28 (66); HRMS calcd for $C_{14}H_{16}O_2$ ([M − t-BuCCOOH]$^+$) 216.1150, found 216.1176.

(1*R*,2*S*,3*S*,6*R*,7*S*,8*S*)-Tricyclo-3-pivaloyloxy[6.2.1.0^{2,7}]-undeca-4-en-6-ol (21b). Recrystallization from hexane gave analytical specimen of **21b**: mp 113−115 °C; IR (KBr) 2968, 1726, 1480, 1396, 1282, 1156, 716 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.18−1.38 (m, 2H), 1.26 (s, 18H), 2.84 (t, J = 1.7 Hz, 2H), 3.05 (dd, J = 1.7, 5.6 Hz, 2H), 5.33 (br s, 2H), 5.33−5.37 (m, 2H), 5.83 (t, J = 1.7 Hz, 2H); MS m/z 346 (M^+, 2), 245 (6), 179 (26), 146 (58), 129 (100), 52 (66); HRMS calcd for $C_{21}H_{30}O_4$ 346.2144, found 346.2137.

***cis*-1-Pivaloyloxy-2-cyclohexanol (22a).** The enantiomeric excess was determined by ^1H NMR in the presence of Eu(hfc)$_3$: IR(neat) 3452, 2940, 1727, 1481, 1287, 1169 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.23 (s, 9H), 1.18−1.90 (m, 8H), 3.82 (m, 1H), 4.95 (dt, J = 3.0, 6.9 Hz, 1H); MS m/z 182 ([M − H_2O]$^+$, 0.5), 98 ([M − t-BuCCOOH]$^+$, 100), 57 (90); HRMS calcd for $C_6H_{10}O$ ([M − t-BuCCOOH]$^+$) 98.0731, found 98.0704.

(1*S*,2*S*,3*R*,6*S*,7*R*,8*R*)-1,8,9,10-Tetrachloro-11,11-dimethoxy-3-pivaloyloxytricyclo[6.2.1.0^{2,7}]undeca-4,9-dien-6-ol (24). The enantiomeric excess was determined by HPLC analysis after oxidation of **24** with PCC into the corresponding ketone using a Daicel CHIRALPAC AS column with a 10:1 mixture of hexane and *i*-PrOH as an eluent solvent. Recrystallization from hexane gave analytical specimen of **24**: mp 62.0−64.0 °C; IR(KBr) 3538, 2960, 1718, 1195, 1151, 1099, 770 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.26 (s, 9H), 3.34 (m 1H), 3.48 (m, 1H), 3.54 (s, 3H), 3.62 (s, 3H), 4.57 (m, 1H), 5.36 (dd, J = 2.7, 7.3 Hz, 1H), 5.60 (d, J = 10.0 Hz, 1H), 5.83 (d, J = 10.3 Hz, 1H); MS *m*/*z* 321/323/325/327 ([M − Cl − *t*-BuCOOH]$^+$, 11/9/4/2), 253/255/257/259 (1-dimethoxycarbonium-2,3,4-trichlorobenzene, 100/96/35/8). Anal. Calcd for $C_{18}H_{22}O_4C_{l4}$: C, 48.67; H, 4.99; Cl, 31.93. Found: C, 48.58; H, 5.05; Cl, 32.18.

(1*S*,2*S*,3*R*,6*S*,7*R*,8*R*)-1,8,9,10-Tetrachloro-11,11-dimethoxy-3,6-dipivaloyloxytricyclo[6.2.1.0^{2,7}]undeca-4,9-diene (24 b): IR (neat) 3005, 1715, 1420, 1363, 1223, 1148, 1093 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.27 (s, 18H), 3.46−3.55 (m, 2H), 3.54 (s, 3H), 3.59 (s, 3H), 5.38 (d, J = 5.3 Hz, 2H), 5.61 (s, 2H); MS *m*/*z* 507/509/511/513 ([M − Cl]$^+$, 19/19/6/1), 43 (100); HRMS calcd for $C_{23}H_{30}O_6Cl_3$ ([M − ^{35}Cl]$^+$) 507.1108, found 507.1090.

(1*S*,2*S*,3*R*,6*S*,7*R*,8*R*)-1,8,9,10-Tetrachloro-11,11-dimethoxy-6-(1-ethoxyethoxy)-3-pivaloyloxytricyclo[6.2.1.0^{2,7}]-undeca-4,9-diene (25). To a solution of monopivalate (250 mg, 0.543 mmol) and pyridinium *p*-toluenesulfonate (40 mg) in dry CH_2Cl_2 (5 mL) was added dropwise ethyl vinyl ether (156 μL, 1.63 mmol) at room temperature. The solution was stirred at room temperature for 45 min. The solution was then washed with water and dried over anhydrous $MgSO_4$. Concentration of the reaction mixture gave a crude product that was purified by column chromatography (Florisil) using a 1:1 mixture of $CHCl_3$ and hexane as an eluent solvent to give pure **25** (284 mg, 98%): IR (neat) 2978, 1733, 1197, 1151, 1052, 786, 772 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.18 (td, J = 3.0, 6.9 Hz, 3H), 1.27 (s, 9H), 1.36 (dd, J = 5.5, 10.1 Hz, 3H), 3.24−3.39 (m, 2H), 3.43−3.67 (m, 2H), 3.54 (s, 3H), 3.60 (s, 3H), 4.49 (m, 1H), 4.88 (dq, J = 5.5, 23.6 Hz, 1H), 5.35 (m, 1H), 5.55 (m, 1H), 5.72 (m, 1H); MS *m*/*z* 495/497/499/501 ([M − Cl]$^+$, 3/3/1/0.2), 73 (100); HRMS calcd for $C_{22}H_{30}O_6Cl_3$ ([M − ^{35}Cl]$^+$) 495.1108, found 495.1137.

(1*R*,2*R*,3*S*,6*R*,7*S*,8*S*)1,8,9,10-Tetrachloro-11,11-dimethoxy-3-(1-ethoxyethoxy)tricyclo[6.2.1.0^{2,7}]undeca-4,9-dien-6-ol (26). To a solution of **26** (230 mg, 0.432 mmol) in MeOH (4 mL) was added 2 M NaOH (1 mL), and the solution was stirred at 50 °C for 64.5 h. Then the solution was neutralized with 2 M HCl and extracted three times with $CHCl_3$. The combined extracts were dried over anhydrous $MgSO_4$. Evaporation of the solvent gave a crude product, which was separated by preparative TLC using a 3:1 mixture of hexane and ethyl acetate as an eluent solvent to yield pure **26** (147 mg, 76%): IR (neat) 3460, 2981, 1184, 1123, 752 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.16 (t, J = 7.1 Hz, 3H), 1.33 (d, J = 5.3 Hz, 3H), 2.85 (dd, J = 4.8, 11.2 Hz, 1H), 3.00 (dd, J = 5.3, 11.2 Hz, 1H), 3.34−3.65 (m, 2H), 3.56 (s, 3H), 3.59 (s, 3H), 4.38 (t, J = 5.3 Hz, 1H), 4.43 (m, 1H), 4.79 (q, J = 5.3 Hz, 1H), 6.32 (dd, J = 5.3, 9.6 Hz, 1H), 6.42 (dd, J = 5.9, 9.6 Hz, 1H); MS *m*/*z* 253/255/257/259 (1-dimethoxycarbonium-2,3,4-trichlorobenzene, 92/89/32/7), 73 (100); HRMS calcd for $C_9H_8O_2Cl_3$ (1-dimethoxycarbonium-2,3,4-trichlorobenzene) 252.9590, found 252.9600.

(1*S*,2*S*,3*R*,6*S*,7*R*,8*R*)-1,8,9,10-Tetrachloro-11,11-dimethoxy-3-*tert*-butyldimethylsilyloxy-6-(1-ethoxyethoxy)-tricyclo[6.2.1.0^{2,7}]undeca-4,9-diene (27). Alcohol **26** (25 mg, 0.056 mmol) was dissolved in 0.5 mL of dry DMF and cooled to 0 °C. To this solution were added 2,6-lutidine (19 μL, 0.16 mmol) and TBDMS triflate (19 μL, 0.083 mmol), and the reaction mixture was stirred at 0 °C for 2.5 h. The reaction was quenched by saturated aqueous $NaHCO_3$ and diluted with water. After extraction with ether, the organic layers were washed once with water and once with brine and dried over anhydrous $MgSO_4$. Evaporation of the solvent gave a crude product that was purified by column chromatography (Florisil) using a 10:1 mixture of hexane and ether as an eluent solvent to give pure **27** (25 mg, 80%): mp 103.6−105.2 °C; IR (KBr) 2953, 1195, 1124, 1082, 796, 777 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.06 (s, 3H), 0.09 (s, 3H), 0.93 (s, 9H), 1.19 (t, J = 7.1 Hz, 3H), 1.34 (d, J = 5.3 Hz, 3H), 3.14 (m, 1H), 3.25 (m, 1H), 3.46−3.71 (m, 2H), 3.54 (s, 3H), 3.61 (s, 3H), 4.43 (m, 2H), 4.93 (q, J = 5.3 Hz, 1H), 5.57 (br s, 2H); MS *m*/*z* 525/527/529/531 ([M − Cl]$^+$, 2/2/0.8/0.2), 253 (100); HRMS calcd for $C_{23}H_{36}O_5Cl_3Si$ ([M − ^{35}Cl]$^+$) 525.1398, found 525.1350.

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Supporting Information Available: Copies of ^{1}H NMR spectra for compounds **2**−**4**, **6**−**8**, **9c**, **10b**,**c**, **11c**, **13c**, **14c**, **15**−**18**, **19a**,**b**, **20a**,**b**, **21b**, **22a**, **24b**, and **24**−**27** and ^{13}C NMR spectra for compounds **3** and **4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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