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Asymmetric oxidation of some 1,3-dithianes in presence of chiral titanium complexes *

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Abstract

Various 2-substituted 1,3-dithianes have been oxidized to the corresponding 1-oxides by cumene hydroperoxide in presence of a titanium complex ($Ti(O\text{-}i\text{-}Pr)_4$/(+)-DET/$H_2O$ = 1/2/1) used in stoichiometric or lesser amounts. Enantioselectivity of up to 80% and excellent diastereoselectivity were achieved by a careful control of experimental conditions. The reaction temperature was found to be an important parameter. The relative stereochemistries of the new substituted monosulfoxides were determined by NMR spectroscopy.

Introduction

We described in 1984 an efficient method for the oxidation of various sulfides to the corresponding monosulfoxides [1,2]. The procedure was based on a modification of the use of the Sharpless reagent ($Ti(O\text{-}i\text{-}Pr)_4$/(+)-DET/t-BuOOH = 1/1/2) for asymmetric epoxidation of allylic alcohols [3]. We found that one molecule of water deactivated this reagent for epoxidation [4], to give a complex active in asymmetric oxidation of sulfides. The best combination for this purpose appeared to be $Ti(O\text{-}i\text{-}Pr)_4$/(+)-DET/$H_2O$/t-BuOOH = 1/2/1/1. Independently Modena et al. [6] found that a large excess of diethyl tartrate modifies the Sharpless reagent to give an asymmetric oxidant system for prochiral sulfides. In recent years we have developed our reagent for enantioselective oxidation of various classes of sulfur compounds [7–12]. A useful modification involved the replacement of t-BuOOH by $Me_2C(Ph)OOH$ (cumene hydroperoxide) [11,12]. In this way we were able to bring about asymmetric oxidation of arylmethylsulfoxides with ee's of up to 95%. Moreover the reaction was carried out with stoichiometric (Ti/Sulfide = 1) or substoichiometric amounts (Ti/Sulfide = 0.5) of the titanium compound. In some cases true catalytic conditions were approached (Ti/Sulfide = 0.2) [12]. We describe here

* Dedicated to the memory of Professor E. Lederer, who without words but with an aura of sympathy knew how to communicate his deep faith in science.

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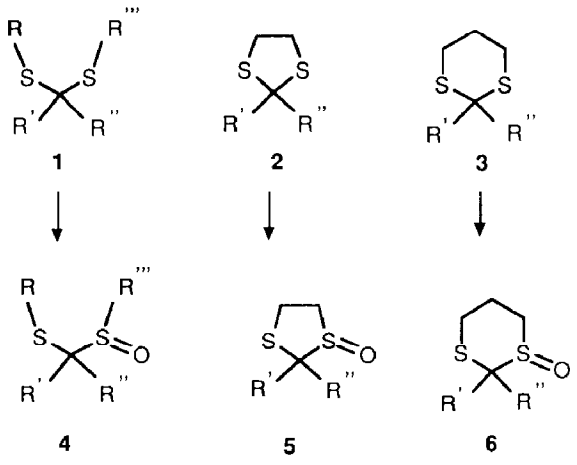


our results in asymmetric oxidation of some 2-substituted 1,3-dithianes by the new method involving use of cumene hydroperoxide.

Previous results on asymmetric oxidation of 1,1-disulfides

There are some examples in literature of asymmetric oxidation at sulfur in thioacetals or thiocetals **1–3**. Some of the monosulfoxides **4–6** are interesting chiral auxiliaries in organic synthesis. In Table 1 are listed the main results obtained by chemical or biochemical oxidation of **1–3**.

Results

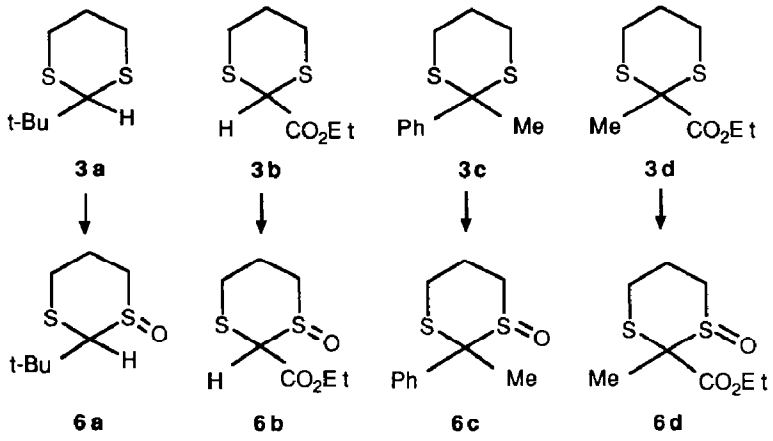
We decided to investigate the asymmetric oxidation of 1,3-dithianes **3** for which there was previously no good oxidant system, either chemical or biochemical (see Table 1).

Table 1

Survey of some asymmetric oxidations of thioacetals or thiocetals into monosulfoxides

Compound		Oxidant system	Diastereom. ratio	ee (%)	Ref.
1	$R' = CH_2CH_2$-phtalimido $R = R''' = Me$ $R'' = H$	A.niger	3/2	46,46	13
3	$R' = H$ $R'' = Me$	Helminthosporium	14/1	27,33	14
3	$R' = Me$ $R'' = t$-Bu	Helminthosporium	100	0	14
3	$R' = R'' = Me$	Helminthosporium		36	14
3a	$R' = H$ $R'' = t$-Bu	Helminthosporium	4/1	35,72	14
1	$R = Me$ $R''' = Ph$ $R' = R'' = H$	C.equi		95	15
1	$R = R' = Me$, $R' = R'' = H$	t-BuOOH/Ti reagent [a]		40	7
3	$R' = R'' = H$	t-BuOOH/Ti reagent [a]		20	7
3	$R' = Ph$ $R'' = H$	t-BuOOH/Tireagent [b]	90/10	14 [c]	16
3c	$R' = Ph$ $R'' = Me$	t-BuOOH/Ti reagent [b]	85/15	39 [c]	16
2	$R' = Ph$ $R'' = Me$	t-BuOOH/Ti reagent [b]	97/3	83 [c]	16
2	$R' = t$-Bu $R'' = Me$	t-BuOOH/Ti reagent [b]	99/1	68 [c]	16
2	$R' = t$-Bu $R'' = H$	t-BuOOH/Ti reagent [b]	99/1	70	16
2	$R' = Ph$ $R'' = H$	t-BuOOH/Ti reagent [b]	94/6	76	16

[a] $Ti(O\text{-}i\text{-}Pr)_4/(+)\text{-DET}/H_2O = 1/2/1$. [b] $Ti(O\text{-}i\text{-}Pr)_4/(+)\text{-DET} = 1/4$. [c] ee of major diastereomer.



1,3-Dithianes **3a**,**3c**,**3d** were readily prepared by treatment of 1,3-propanedithiol with aldehydes or ketones at 0 °C in the presence of $BF_3 \cdot Et_2O$. Compound **3b** (**3**: $R' = CO_2Et$, $R'' = H$) is commercially available.

The initial experiments were carried out on **3a** and **3c** under our standard conditions [12], in methylene chloride with cumene hydroperoxide in presence of 1 mol.eq of the water-modified reagent (Ti(O-i-Pr)$_4$/(+)-diethyl tartrate (DET)/$H_2O = 1/2/1$). The monosulfoxides **6a** and **6c** were obtained in good yields. Product **6a** was a mixture of *cis-trans* diastereomers (10/90), whereas **6c** was diastereomerically pure. Sulfoxides **6a** (*cis* and *trans*) were racemic, and **6c** showed 78% ee. In order to try to improve the enantiomeric excess a detailed study of the temperature dependence was carried out with sulfide **3b**. It was found that **3b** always gives a 40/60 mixture of *cis* and *trans* sulfoxides **6b**, with the same ee for *cis*

Table 2

Asymmetric oxidation of dithianes **3a–3d** into monosulfoxides **6**

Dithiane	Reaction temp. [a] (°C)	Isolated yield [b] (%) in **6**	*trans*/*cis* ratio	$[\alpha]_D$ (°)	ee [e] (%)
3a	−23	97	90/10		0
3a	−35	44	90/10		0
3a	−78	49	90/10		0
3b	−23	50	60/40		30
3b	−40	65	60/40		80
3b	−50	70	60/40		64
3b	−78	50	60/40		5
3c	−40	49	100/0	+18.9 [c]	78
3c	−78	53	100/0	+13.5 [c]	57
3d	−38	65	100/0	+76 [d]	80

[a] Oxidation by one mole.eq of cumene hydroperoxide in the presence of titanium complex (Ti(O-i-Pr$_4$/(+)-DET/$H_2O = 1/2/1$). One mol.eq of titanium complex was used in the case of **3a** and **3c**, 0.5 mol.eq of titanium complex was used for oxidation of **3b** or **3d**. Solvent: CH_2Cl_2. See ref. 12 for details of the general procedure. Reaction time 50 h. [b] Product is isolated after hydrolysis and flash-column chromatography, as described for other cases in ref. 12. [c] In ethanol. [d] In CH_2Cl_2 ($c = 1$). [e] Measured by NMR spectroscopy with Eu(hfc)$_3$ as chiral shift reagent.

and *trans* **6b**. However the enantiomeric excess is strongly dependent on the reaction temperature (30% ee at −23°C, 80% ee at −40°C, 64% ee at −50°C and 5% ee at −78°C). It was established (see below) that the absolute configuration is the same at sulfur for *cis* or *trans* **6b**. In the oxidation of **3a** the *cis/trans* ratio is independent of the temperature. Compounds **3c** and **3d** give exclusively *trans* sulfoxides at −38°C, and a very good ee (80%) was achieved. An enantiomeric excess of 78% in *trans*-**6c** was similarly obtained at −40°C, while at −78°C the ee was 57%.

Stereochemical assignments for the sulfoxides 6a–6d

Trans and *cis* sulfoxides **6a** have been prepared (as racemic mixtures) by oxidation of **3a** (*trans/cis* = 9/1) with sodium metaperiodate [17,18]. Comparison of NMR data shows that the major sulfoxide produced in the asymmetric oxidation has *trans* stereochemistry. The ^{13}C NMR spectrum unambiguously shows that the sulfinyl and the t-butyl groups are both equatorial, while in the *cis* stereoisomer the sulfinyl group is axial and the t-butyl group equatorial. These conclusions are based on the characteristic ^{13}C chemical shift for C(5) [19] and the ^{1}H chemical shifts of the 2-axial protons [18] (Table 3).

Table 3

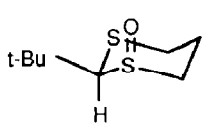
NMR data of 2-substituted 1,3-dithianes 1-oxides (ppm from TMS)

	^{13}C NMR					^{1}H NMR				
	C(2)	C(4)	C(5)	C(6)	substituent at C(2)	H(2)	H(4)	H(5)	H(6)	substituent at C(2)
trans-**6a**	76.8	29.8	30.2	55.4	28.3 (Me) 36 (C t-Bu)	3.57 2-ax	2.4 2.6	2.2 2.4	2.75 3.4	1.2 (t-Bu)
(ref. [18] ^{1}H [19] ^{13}C)										
cis-**6a**	73.8	29.7	14.4	47.7	28.3 (Me) 36 (C t-Bu)	3.4 2-ax	2.4 2.6	1.7 2.6	2.9 3.1	1.15 (t-Bu)
(ref. [18] ^{1}H [19] ^{13}C)										
trans-**6b**	64.2	28	24	62.8	13.9 (Me) 50 CH_2 165.6 COO	4.3	2.6 2.85	2.1 2.6	2.85 3.4	
cis-**6b**	62.4	25.6	24	55.5	13.9 (Me) 46.3 CH_2 166 COO	4.6	2.5 3	2.2 2.3	3.2 3.6	
trans-**6c**	64.5	22.6	26.2	45	18.6	–	2.7	2.1 2.5	2.85	1.97 (Me)
(ref. [19] ^{13}C)					(Me axial)					
cis-**6c**	65.5	28.4	27.3	47	27.8					
(ref. [19] ^{13}C)					(Me equat.)					
trans-**6d**	64.4	26	16.2	62.5	18.9 (Me) 13.8 (Me) 45 CH_2 169 COO	–	2.5 2.85	1.8 2.4	3 3.15	1.7 (Me)
cis-**6d**	61.15	28.4	27.2	62.5	21.24 (Me) 14.1 (Me) 47.8 CH_2 167.5 COO		2.25 3.1	2.3 2.35	3.55 3.55	1.85 (Me)

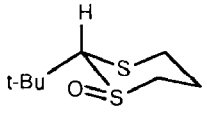
Sulfoxides **6c** (*cis* and *trans*) have been previously prepared [19] and stereochemical assignments made by use of ^{13}C NMR data. From a comparison of the ^{13}C NMR spectrum of the monosulfoxide **6c** obtained by asymmetric oxidation with data in ref. 19, we conclude that our reaction gives only the *trans* stereoisomer (phenyl is *trans* with respect to oxygen), with the sulfinyl group equatorial.

The relative stereochemistry of sulfoxides **6b** and **6d** are unknown. We established the stereochemistry in the following way of the compounds that we isolated. The two diastereomers of **6b** must have an equatorial sulfinyl group, because in both compounds the chemical shift of C(5) is 24 ppm (instead of 15 ppm when S=O is axial). The orientation (axial or equatorial) of the CO_2Et group is difficult to determine. The chemical shifts of H(2) in the epimers are different (4.6 and 4.3 ppm). By analogy with reasoning in ref. 20, we assign an equatorial position to the more deshielded proton and so an axial orientation in the case of the other epimer. On this basis the predominant diastereomer is thought to be *trans*-**6b**.

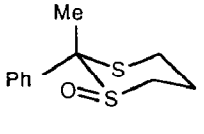
Oxidation of **3d** only gave one sulfoxide. In order to consider its stereochemistry we prepared its epimer by methylation of **6b** (deprotonation by LDA and addition of methyl iodide). The stereoselectivity of methylation is complete (> 98%). Comparison of ^{13}C NMR data for the sulfoxides **6d** obtained by oxidation with those made by methylation indicates a *trans* relationship between CO_2Et and S=O (*trans*-**6d**) for the oxidation compound and so *cis*-**6d** must be the product of C-methylation of **6c**. The ^{13}C NMR spectra indicates that the S=O group is equatorial in *cis*-**6d** (δ(C(5)) = 27.2 ppm) but axial in *trans*-**6d** (δ(C(5)) = 16.2 ppm). If we assume as a general feature a shielding of an alkyl substituent *cis* to S=O (by respect to a *trans* substituent) in sulfoxides **6** [20], we can tentatively conclude that the sulfoxide produced by oxidation is *trans*-**6d** ($\delta(CH_3)(2) = 18.9$ ppm, against $\delta = 21.24$ ppm for the diastereomer). The various structures and conformations of sulfoxides **6** discussed in this section are indicated:



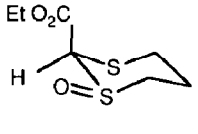
cis - **6a**



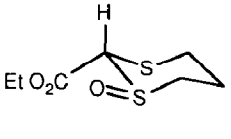
trans - **6a**



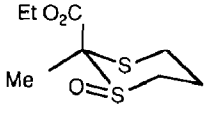
trans - **6c**



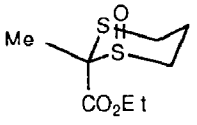
cis - **6b**



trans - **6b**



cis - **6d**



trans- **6d**

Absolute configuration of the monosulfoxides 6a–6d

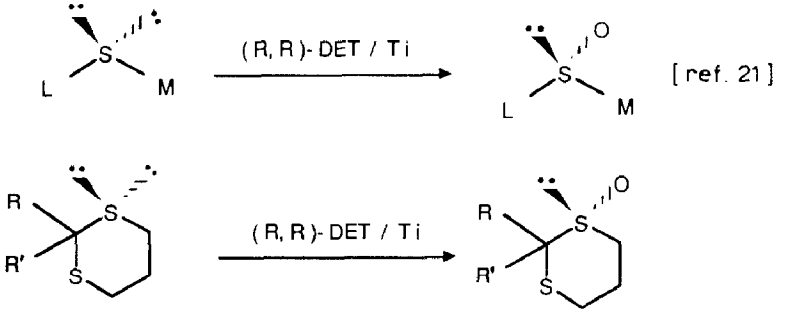
It was only recently that the absolute configurations of some 1,3-dithiane 1-oxides were established by the combined use of X-ray crystallography and CD

[14,21]. It appears that almost all the 2-alkyl 1,3-dithiane-1-oxides have a specific rotation directly related to the absolute configuration at sulfur: a dextrorotatory sulfoxide has the (*R*)-configuration at sulfur [21]. On this basis sulfoxides **6b**, **6c**, and **6d** we generated by asymmetric oxidation have the (*R*)-configuration at sulfur. This is consistent with our earlier result [7] for oxidation of **3** ($R' = R'' = H$) into (+)-**6** ($R' = R'' = H$), which is known to have (*R*)-configuration [21]. The *cis–trans* distribution of sulfoxides observed during oxidation of **3b** (Table 2) is not affected by the oxidation process. We found that pure *trans*-(+)-**6b** kept in presence of $Ti(O\text{-}i\text{-}Pr)_4$ at $-23°C$ and then recovered after hydrolysis gave rise to a *cis–trans* mixture with the same composition as the crude product from an asymmetric oxidation at $-23°C$ and with an enantiomeric excess of the *trans* starting material. This shows that the sulfoxides **6b** have an acidic hydrogen at C(2) which permits in situ formation of a titanium enolate. The absolute configuration at sulfur in the two sulfoxides is then identical, but we have no information about the actual diastereomer distribution under conditions of kinetic control.

Conclusion

A study of the effect of varying the temperature of reaction has allowed us to prepare various types of 2-substituted 1,3-dithiane-1-oxides with enantiomeric excesses of up to 80% (at sulfur of sulfinyl moiety). Moreover sulfoxides **6c** and **6d** (which have no mobile hydrogen at C_2) were obtained diastereomerically pure. The relative stereochemistry of **6c** has already been established [19], and we propose a *trans* stereochemistry for **6d** prepared by oxidation, but this has yet to be confirmed. It seems that the absolute configuration of the predominant sulfoxide can be predicted by use of our Scheme 1, where the "large" group L is the 2-substituted carbon atom.

It is too early to suggest a detailed mechanistic picture of the asymmetric oxidation by cumene hydroperoxide in presence of our titanium reagent. Synthetic aspects of asymmetric synthesis of 1,3-dithianes 1-oxide will be investigated further. Compounds of this type have already been used as chiral auxiliaries in the synthesis of natural products (e.g. asymmetric synthesis of lipoic acid [23]).



Scheme 1

Experimental

Apparatus

^1H and ^{13}C NMR spectra were recorded on Bruker AM 250 MHz spectrometer. Optical rotations were measured on a Perkin–Elmer 241 polarimeter.

Chemicals

CH_2Cl_2 was distilled over calcium hydride and stored under argon over a molecular sieve. Cumene hydroperoxide(CHP) 80% (Aldrich Co), 1,3-propanedithiol (Merck) and 1,3-dithiane-2-carboethoxy **3b** (Janssen Co) were from commercially suppliers and were used as supplied. $Ti(O\text{-}i\text{-}Pr)_4$ (Aldrich Co) and (+)-diethyl tartrate (Janssen Co) were distilled and stored under argon. Silica gel (Merck, 230–400 mesh) was used for flash column chromatography.

As described in ref. 22, 1,3-dithiane **3c** was prepared in 66% yield, from acetophenone and 1,3-propanedithiol, **3a** from pivalaldehyde in 40% yield, and **3d** from ethyl pyruvate in 30 yield. The NMR spectra of **3a–3c** are in agreement with published data.

3d is purified by flash chromatography (AcOEt–cyclohexane) and has the following spectrum: $\delta(^1H)$ (ppm): 2.6 (2H,H(4)); 1.85 and 2.15 (2H, H(5)); 3.4 (2H, H(6)); 1.85 (CH_3). Analysis **3d**: Found: C, 46.7; H, 6.9; O, 15.6; S, 31.3. $C_8H_{14}O_2S_2$ calc: C, 46.6; H, 6.8; O, 15.5; S, 31.1%.

Asymmetric oxidations

These were performed as described previously [12]. As an example we describe the sub-stoichiometric oxidation of **3b** to **6b**. (+)-(*R*,*R*)-DET (4.25 ml, 25 mmol) was dissolved at room temperature in 150 ml CH_2Cl_2 under argon, then $Ti(O\text{-}i\text{-}Pr)_4$ (3.7 ml, 12.5 mmol) was added with stirring through a septum from a syringe, and H_2O (225 μl, 12.5 mmol) was then added carefully so that the drops fell within the vortex formed by the stirring bar. The solution became yellow; it was stirred for a further 20 min and then sulfide **3b** (4.8 g, 25 mmol) was added. The solution was kept at −40 °C for 1 h, and CHP (80%) (5 ml, 25 mmol) then introduced, and the mixture kept at −40 °C for 48 h with stirring. Water (5 ml) was added and vigorous stirring maintained for 1 h at room temperature. The white gel was filtered through Celite, and the residue on the Celite was thoroughly washed with CH_2Cl_2. The filtrate was dried, concentrated and flash-chromatographed on silica-gel with AcOEt as eluant. 2-Phenyl isopropanol was separated first along with the remaining sulfide, followed by **6b** (3.5 g; 70%).

Analysis **6b**: Found: C, 40.4; H, 5.9; O, 23.3; S, 30.4. $C_7H_{12}O_3S_2$ calc: C, 40.4; H, 5.8; O, 23.1; S, 30.7%.

^1H and ^{13}C NMR: cf. Table 3; 60% *trans* compound, 40% *cis*. The ee was determined by NMR spectroscopy in the presence of $Eu(hfc)_3$ (0.2 equivalent) by use of the H(2) chemical shift. For this oxidation temperature (−40 °C) the ee was 80% for each isomer.

Many recrystallizations in hexane and ether yielded isomerically and enantiomerically pure samples: *trans*-**6b**: $[\alpha] = +78°$ ($c = 1$, $CHCl_3$); *cis*-**6b**: $[\alpha] = +183°$ ($c = 1$, $CHCl_3$). *Trans*-**6d**: The same oxidation procedure was used with sulfide **3d**, and led to a single (diastereomerically) pure product, which is believed to be the *trans* isomer (^1H and ^{13}C NMR data in Table 3). ee = 78% (NMR), $[\alpha]_d = +76°$ ($c = 1$, CH_2Cl_2). Analysis: *trans*-**6d**. Found: C, 43.3; H, 6.5; O, 21.6; S, 28.6. $C_8H_{14}O_3S_2$ calc: C, 43.2; H, 6.3; O, 21.6; S, 28.8%. $[\alpha] = +98°$ ($c = 1$, CH_2Cl_2) (calculated for 100% ee).

*Action of $Ti(OiPr)_4$ on **6b***

A *cis-trans* mixture of **6b** prepared by asymmetric oxidation at −23 °C (*cis*/*trans* = 40/60:, 30% ee (+) for each diastereomer) was recrystallized from a

hexane/ether mixture. Along with fractions with various enantiomeric excesses, pure *trans*-**6b** (30% ee) could be isolated. 25 mmol of this sample was stirred for 2 d at −23°C with 2.5 mmol of $Ti(O\text{-}i\text{-}Pr)_4$ in dichloromethane. After hydrolysis with aqueous NH_4Cl and the usual work-up, a *cis/trans* mixture of **6b** (40/60) was isolated. Each diastereomer has 30% ee (as measured by NMR). This result supports the hypothesis that a titanium enolate is formed in situ after oxidation, the *cis–trans* distribution arising at the hydrolysis stage.

C-methylation of ***6b*** *into cis-***6d**

2 mmol of *cis–trans* mixture of **6b** prepared by asymmetric oxidation at −38°C (*cis/trans* = 40/60, 70% ee for each diastereomer) was added to 2.2 mmol of LDA at −60°C in THF and the mixture was stirred for 30 min. Iodomethane (10 mmol) was then added and the mixture allowed to warm to room temperature. The usual work-up and purification by flash chromatography (AcOEt) gave 300 mg (75%) of a single pure product, believed to be the *cis* isomer. (^1H and ^{13}C NMR spectral data are given in Table 3). $[\alpha]_D = +98°$ ($c = 1$, CH_2Cl_2) 65% ee (NMR). Analysis: *cis*-**6d**. Found: C, 43.5; H, 6.3; O, 2.2; S, 28.2. calc: C, 43.2; H, 6.3; O, 21.6; S, 28.8%. $[\alpha] = +150°$ ($c = 1$, CH_2Cl_2) (calculated for 100% ee).

Acknowledgement

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