A Novel Asymmetric Desymmetrisation of *meso*-Cyclopentane-1,2-diol *via* Diastereoselective β-Elimination of Chiral α-Arylsulfinyl Acetals

Naoyoshi Maezaki, Motohiro Soejima, Miwako Takeda, Atsunobu Sakamoto, Tetsuaki Tanaka and Chuzo Iwata*

Faculty of Pharmaceutical Sciences, Osaka University 1-6 Yamadaoka, Suita, Osaka 565, Japan

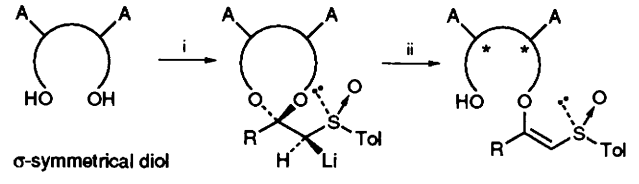
meso-Cyclopentane-1,2-diol was differentiated *via* diastereoselective C–O bond fission of the acetal utilising the anion stabilised by a neighbouring chiral sulfinyl group to provide the chiral alcohol.

Asymmetric desymmetrisation of the diols with σ symmetry is a fascinating methodology to synthesise versatile chiral building blocks for various natural products. Therefore, considerable efforts have been made to develop efficient methods.[1] Although there are a lot of examples of enzymatic differentiation, chemical differentiation is not so well established.

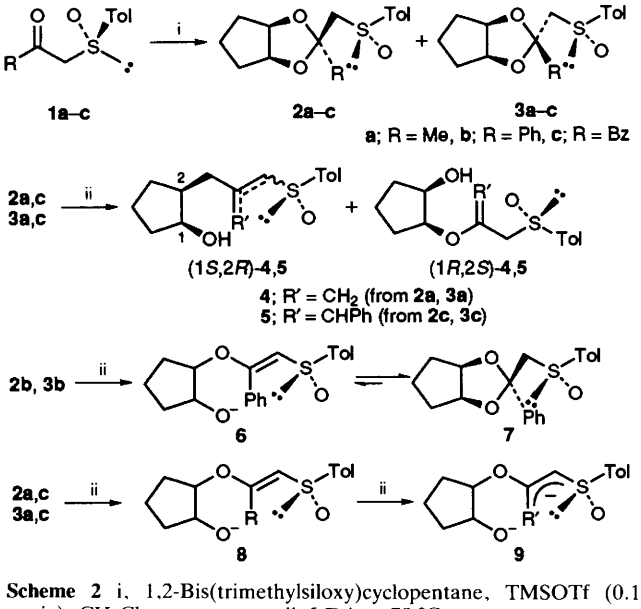
In previous work, we reported a non-enzymatic asymmetric desymmetrisation of prochiral 1,3-diols *via* acetalisation with an intramolecular chiral β-ketosulfoxide moiety followed by diastereoselective acetal fission.[1d] These results prompted us to investigate the potency of the β-ketosulfoxides as reagents to discriminate between the enantiotopic groups of σ-symmetrical diols.

Our strategy was outlined in Scheme 1. The σ-symmetrical diols are first transformed into the chiral α-sulfinyl acetals. The chiral α-sulfinyl carbanions[2] can then differentiate between enantiotopic groups of *meso*-diols *via* diastereoselective β-elimination. Herein we report the novel asymmetric desymmetrisation of *meso*-cyclopentane-1,2-diol utilising diastereoselective β-elimination of the chiral α-sulfinyl acetal.

Chiral α-sulfinyl acetals were synthesised *via* condensation of the bis(trimethylsilyl) ether of *cis*-cyclopentane-1,2-diol with the β-ketosulfoxides **1a–c** in the presence of trimethylsilyl trifluoromethanesulfonate (TMSOTf) catalyst as shown in Scheme 2 (**2a** 59%, **3a** 30%, **2b** 0%, **3b** 74%, **2c** 24%, **3c** 48%).[3] The configurations of the resulting acetals were determined by the observation of NOE between the angular methine protons of the bicyclic ring and the substituent R or the sulfinylmethyl group.



Scheme 1 i, Chiral α-sulfinyl acetal; ii, diastereoselective β-elimination. Tol = *p*-MeC_6H_4



Scheme 2 i, 1,2-Bis(trimethylsiloxy)cyclopentane, TMSOTf (0.1 equiv), CH_2Cl_2, room temp.; ii, LDA, −78 °C

Upon treatment with 6 equiv. of lithium diisopropylamide (LDA) at −78 °C, the acetals **2a** and **3a** yielded the alcohols (1*S*,2*R*)- and (1*R*,2*S*)-**4** within 30 min as shown in Table 1. (1*S*,2*R*)-**4** was a mixture of the β,γ- and α,β-unsaturated sulfoxides. The absolute configurations of these products were determined by Mosher's method.[4] It is interesting that both **2a** and **3a** were diastereoselectively converted into (1*S*,2*R*)-**4**. The selectivity of the cleavage in **3a** was higher than that in **2a**.

On the other hand, acetal **3b** did not provide products arising from acetal cleavage, but isomerised to **2b** in 88% yield on treatment with 6 equiv. of LDA in THF at −78 °C. The resulting species **2b** proved to be unreactive.

In contrast with the phenyl derivatives **2b** and **3b**, the benzyl derivatives **2c** and **3c** afforded the chiral alcohols (1*S*,2*R*)- and (1*R*,2*S*)-**5**[4] upon use of only 3 equiv. of base. In these cases, the α,β-unsaturated sulfoxide was not produced. The selectivity was generally higher than that found for **2a** and **3a**. Fairly good selectivity was observed when 3 equiv. of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) was added or DME was used as a solvent, except for **3c** in DME.

The different reactivity of the α-sulfinyl acetals may be explained as follows. For acetals **2b** and **3b** (R = Ph), recyclisation predominates over ring cleavage since the equilibrium between **6** and **7** is strongly shifted towards **7**. On the other hand, the monoanions **8** (R = Me or Bzl) resulting from the acetals **2a**, **2c**, **3a**, and **3c** are further deprotonated to give the dianions **9**, in which recyclisation would be prevented by repulsion between the anions.† Since the γ-position of the sulfinyl group in **2c** and **3c** is more acidic than that in **2a** and **3a**, a smaller amount of base is required to form the dianion **9**.

The diastereoselectivity of acetal fission can be explained as follows (Fig. 1). The *p*-tolyl group would be *anti* to a bulky bicyclic ring. In the case of **3a** and **3c**, conformer **I** would predominate over conformer **II** since the partially positive sulfur atom benefits from the so-called attractive *gauche* interaction[5] with the partially negative acetal oxygens in **I**. In

Table 1 Diastereoselective acetal cleavages with LDA

Acetal	Equiv. of LDA (solvent)	Yield (%)[a]	Cleavage ratio[b] (1*S*,2*R*)	(1*R*,2*S*)
2a	6 (THF)	95	74[c]	26
2a	6 (DME)	69	81[c]	19
3a	6 (THF)	81	82[c]	18
3a	6 (DME)	83	89[c]	11
2c	3 (THF)	92	86[d]	14[e]
2c	3 (TMEDA–THF)	92	84[d]	16[e]
2c	3 (DME)	92	90[d]	10[e]
3c	3 (THF)	91	90[f]	10[g]
3c	3 (TMEDA–THF)	92	94[f]	6[g]
3c	3 (DME)	92	48[f]	52[g]

[a] Total yield. [b] The ratio was determined by 200 MHz ^1H NMR spectroscopy. [c] The ratio of β,γ- and α,β-unsaturated sulfoxide ranged from 2 : 1 to 7 : 1. [d] *E*/*Z* = 1/1–1/3. [e] *E*/*Z* = 4/1–1/2. [f] *E*/*Z* = 1/8–1/43. [g] *E*/*Z* = 2/1–1/12.

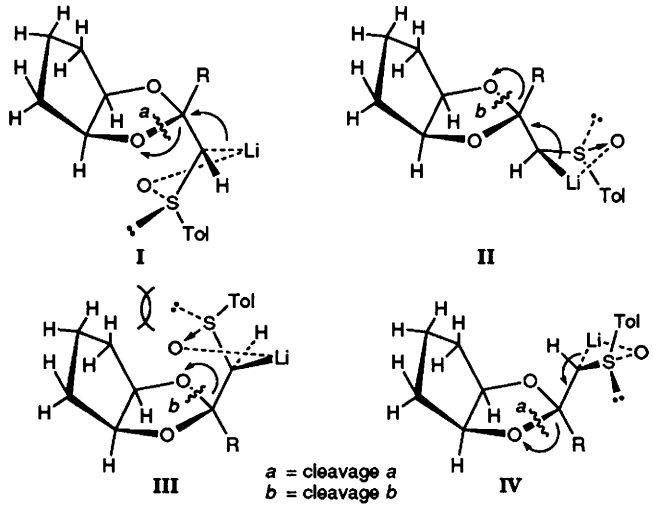


Fig. 1

contrast, conformer **II** is destabilised by an unfavourable *gauche* interaction between the sulfinyl group and the bulky substituent R. Consequently, cleavage *a* would precede cleavage *b* owing to diastereoselective deprotonation of the pro-*S* proton (a proton *gauche* to the sulfinyl oxygen),‡ followed by *anti* elimination. In the case of **2a** and **2c**, the conformer **IV** would be more favourable than **III** since the steric repulsion between the cyclopentane ring and the sulfinylmethyl group in **III** is of more significance than the *gauche* interaction between the sulfinyl group and R in **IV**. As a result, cleavage *a* predominates over cleavage *b*.§

Further investigations into the mechanism and applications are now under way and the results will be reported in the near future.

This work is partially supported by grants-in-aid sponsored by the Ministry of Education, Science and Culture (No. 05771926).

Received, 9th February 1994; Com. 4/00808A

Footnotes

† Formation of the dianion intermediates **9** were supported by the deuteriation of the α-position to the sulfinyl group in **2a** and **3a** upon treatment with D_2O.

‡ Highly diastereoselective hydrogen–deuterium exchange has been observed at the α-position of the chiral sulfoxide. That is, an α-proton which is *gauche* to the S–O bond and *trans* to the lone pair on sulfur is lithiated more rapidly than others. The stereochemical outcome was explained by Ohno and coworkers[2a] as follows; (*i*) feasibility of deprotonation due to the *anti* relationship between the electronegative sulfinyl lone pair and the resulting carbanion and (*ii*) stability of the carbanion owing to chelation with sulfinyl oxygen.

§ Sakai and coworkers[1a,b] have recently reported diastereoselective acetal fission using a chiral ester as the chiral auxiliary. In these reports, they suggested that a thermodynamically stable anion was produced. We could not exclude the possibility that our reaction was also thermodynamically controlled. However, we assume that our reaction was kinetically controlled from the following reasons: (*i*) the diastereoisomers of acetals showed differring selectivity in the acetal cleavage reaction and (*ii*) (1*S*,2*R*)- and (1*R*,2*S*)-**4** did not afford the equilibrium mixture on treatment with base, with the materials recovered unchanged.

References

1 For chemical methods: (*a*) H. Suemune, K. Watanabe, K. Kato and K. Sakai, *Tetrahedron: Asymmetry*, 1993, **4**, 2109; (*b*) K. Sakai and H. Suemune, *Tetrahedron: Asymmetry*, 1993, **4**, 1767; (*c*) C. Iwata, N. Maezaki, K. Hattori, M. Fujita, Y. Moritani, Y. Takemoto, T. Tanaka and T. Imanishi, *Chem. Pharm. Bull.*, 1993, **41**, 339, 946; (*d*) C. Iwata, N. Maezaki, M. Murakami, M. Soejima and T. Tanaka, *J. Chem. Soc., Chem. Commun.*, 1992, 516; (*e*) R. S. Ward, *Chem. Soc. Rev.*, 1990, **19**, 1; (*f*) C. Iwata, M. Fujita, Y. Moritani, K. Hattori and T. Imanishi, *Tetrahedron Lett.*, 1987, **28**, 3135; (*g*) C. Iwata, M. Fujita, Y. Moritani, K. Sugiyama, K. Hattori and T. Imanishi, *Tetrahedron Lett.*, 1987, **28**, 3131; (*h*) M. Nara, S. Terashima and S. Yamada, *Tetrahedron*, 1980, **36**, 3161, 3171 and references cited in ref. 1(*d*). For enzymatic methods: reviews, (*i*) G. Guanti, L. Banfi, C. Ghiron and E. Narisano, *Tetrahedron Lett.*, 1991, **32**, 267; (*j*) J. Mulzer, H.-J. Attenbach, M. Braun, K.Krohn and H.-U. Reissing, in *Organic Synthesis Highlight*, VCH, New York, 1991, p. 224; (*k*) L.-M. Zhu and M. C. Tedford, *Tetrahedron*, 1990, **46**, 6587; (*l*) Z.-F. Xie, *Tetrahedron: Asymmetry*, 1991, **2**, 733; (*m*) D. Scebath, *Angew. Chem., Int. Ed. Engl.*, 1990, **29**, 1320; (*n*) M. Ohno and M. Otsuka, *Org. React.*, 1989, **37**, 1.

2 (*a*) K. Nakamura, M. Higaki, S. Adachi, S. Oka and A. Ohno, *J. Org. Chem.*, 1987, **52**, 1414; (*b*) K. Ogura, in *Comprehensive Organic Synthesis*, ed. B. M. Trost and I. Fleming, Pergamon, 1991, vol. 1, p. 505 and references cited therein.

3 T. Tsunoda, M. Suzuki and R. Noyori, *Tetrahedron Lett.*, 1980, **21**, 71.

4 J. A. Dale and H. S. Mosher, *J. Am. Chem. Soc.*, 1973, **95**, 512; *J. Org. Chem.*, 1969, **34**, 2543.

5 E. Juaristi, *J. Chem. Educ.*, 1979, **56**, 438; E. Juaristi, in *Introduction to Stereochemistry and Conformational Analysis*, Wiley, New York, 1991, ch. 16, p. 271.