Preparation of Optically Active 5-Alkoxyfuran-2(5H)-ones and 5-Methoxy-dihydrofuran-2(3H)-one by Chiral Inclusion Complexation

Fumio Toda,*[a] Koichi Tanaka,[a] Chiu W. Leung,[b] Auke Meetsma[b] and Ben L. Feringa*[b]

[a] Department of Applied Chemistry, Faculty of Engineering, Ehime University, Matsuyama, Ehime 790, Japan
[b] Department of Organic and Molecular Inorganic Chemistry, Groningen Centre of Catalysis and Synthesis, University of Groningen, Nijenborgh 4, NL-9747 AG Groningen, The Netherlands

Racemic 5-alkoxyfuran-2(5H)-ones and 5-methoxydihydrofuran-2(3H)-one are resolved by inclusion complexation employing a crystallization or suspension method with tartaric acid-derived chiral hosts.

Optically active 5-alkoxyfuran-2(5H)-ones 1 (butenolides) are important chiral synthons owing to their multifunctional nature and diversity in enantioselective transformation reactions, e.g. cycloadditions, enolate and acetal chemistry and conjugate addition reactions.[1] So far chiral auxiliary-based (+)- or (−)-menthyloxy butenolides 1 (R = menthyl) have been employed[1,2] but an easy route to enantiomerically pure 1 (R = alkyl) would be highly desirable. The use of optical resolution of various racemic guest compounds by inclusion crystallization in optically active host compounds has been highly successful.[3]

We now report on an easy and efficient preparation of optically active butenolides 1 by resolution of racemic 1 through inclusion complexation with chiral host compounds 3–5 derived from tartaric acid. This resolution method was also found to be applicable to 5-methoxydihydrofuran-2(3H)-one 2.

Both recrystallization (A) and suspension (B)[4] methods can be employed. The results of optical resolutions are summarized in Table 1. As well as efficient resolution of all the host compounds, several interesting features are observed. For example, 1b was efficiently resolved through an enantioselective inclusion complexation with chiral host 3 by both simple recrystallization and by suspension in water of the chiral host and racemic 1b. However, 1b did not form any inclusion complex with the host 5 by the suspension method although it was effectively resolved by the recrystallization method. Intriguingly, the n-propyloxy derivative 1c was resolved with the host 3 by the suspension method but not by the recrystallization method. Furthermore, it is interesting that (+)-1b is complexed enantioselectively with the host 3 while (−)-1b is complexed with the host 5.

Thus, when a solution of (R,R)-(−)-trans-2,3-bis(hydroxy-diphenylmethyl)-1,4-dioxaspiro[5.4]decane 3[5] (2.0 g, 3.95

mmol) and racemic 1b (1.01 g, 7.89 mmol) in toluene–hexane (1:1; 20 ml) was kept at room temperature for 24 h, a 1:1 inclusion complex was obtained as colourless needles (1.74 g), which upon heating in vacuo (220 °C at 20 mmHg) gave (+)-1b in 88% enantiomeric excess (ee)† {0.16 g, 32% yield, [α]$_D$ +84.6 (c 0.55, MeOH)} (entry 5 in Table 1). Similarly, when a suspension of finely powdered 3 (1.5 g, 1.98 mmol) and racemic 1b (0.51 g, 3.98 mmol) in water (10 ml) containing hexadecyltrimethylammonium bromide (0.05 g) as a surfactant was stirred at room temperature for 6 h, a 1:1 inclusion complex of 3 and (+)-1b was formed as crystals, which upon
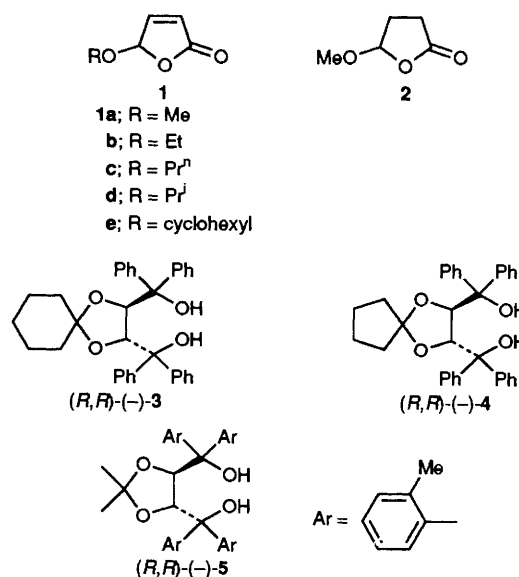

1
1a; R = Me
b; R = Et
c; R = Pr^n
d; R = Pr^i
e; R = cyclohexyl

2

(R,R)-(−)-3

(R,R)-(−)-4

(R,R)-(−)-5

Ar =

Table 1 Optical resolution of 1 and 2 by complexation with the chiral hosts 3–5 via recrystallization (A) or suspension (B) methods

Entry	Host	Guest	Method	Product	Yield (%)	Optical purity (% ee)
1	3	1a	A	(+)-1a	91	18[a]
2	3	1a	B	—[b]		
3	5	1a	A	(−)-1a	41	92[c]
4	5	1a	B	—[b]		
5	3	1b	A	(+)-1b	32	88[a]
6	3	1b	B	(+)-1b	24	98[a]
7	5	1b	A	(−)-1b	10	100[c]
8	5	1b	B	—[b]		
9	3	1c	A	(−)-1c	55	2[a]
10	3	1c	B	(−)-1c	25	94[a]
11	3	1d	A	(+)-1d	45	82[a]
12	3	1d	B	(+)-1d	46	90[a]
13	4	1e	A	(+)-1e	68	92[c]
14	4	1e	B	—[b]		
15	5	2	A	(−)-2	50	96[c]
16	5	2	B	—[b]		

[a] Inclusion crystal is too unstable to purify by recrystallization. [b] No complexation occurred. [c] Inclusion crystal is stable and can be purified by recrystallization. From the purified crystal, optically pure guest was obtained by distillation.
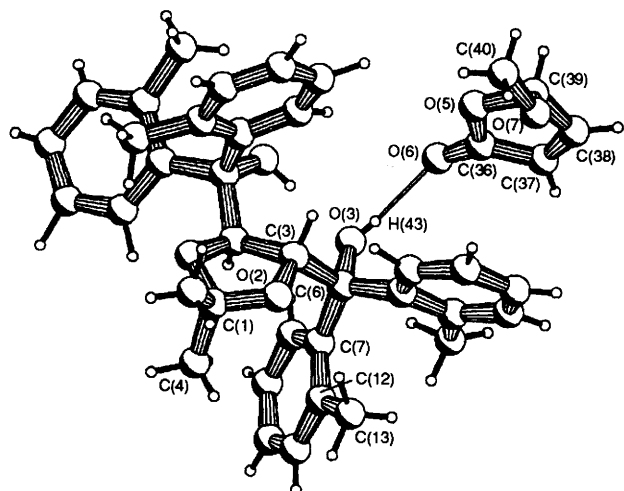
Fig. 1 PLUTO diagram of the 1 : 1 inclusion complex of 5 and 1a with adopted atom numbering scheme. Selected bond lengths (Å) and angles (°), with esds in parentheses: C(1)–C(4) 1.484(8), C(1)–O(2) 1.454(5), C(3)–O(2) 1.444(6), C(3)–C(6) 1.550(6), C(6)–O(3) 1.452(6), C(6)–C(7) 1.537(7), C(7)–C(12) 1.399(8), C(12)–C(13) 1.482(9), O(3)–H(43) 0.73(6), H(43)–O(6) 2.00(6), C(36)–O(6) 1.215(6), C(36)–C(37) 1.441(8), C(37)–C(38) 1.303(9), C(38)–C(39) 1.492(8), O(5)–C(36) 1.362(6), O(5)–C(39) 1.457(6), C(39)–O(7) 1.382(6), O(7)–C(40) 1.437(8); O(3)–H(43)···O(6) 174(6), C(39)–O(7)–C(40) 112.8(4), O(5)–C(36)–O(6) 120.5(5), O(3)–C(6)–C(3) 103.1(3), O(3)–C(6)–C(14) 106.3(3), C(6)–C(14)–C(15) 121.3(4).

heating *in vacuo* (220 °C at 20 mmHg) gave (+)-**1b** in 98% ee {0.06 g, 24% yield, [α]$_D$ +92.8 (*c* 0.45, MeOH)} (entry 6). Using the recrystallization method for a combination of (*R,R*)-(−)-*trans*-4,5-bis(hydroxydi-*o*-tolylmethyl)-2,2-dimethyl-1,3-dioxa-cyclopentane **5** and racemic **1b**, (−)-**1b** of 100% ee was obtained (entry 7).

Although **1a** was only modestly resolved with **3** by the recrystallization method (entry 1) and did not form an inclusion complex with **3** by the suspension method (entry 2), it was resolved efficiently with **5** by the recrystallization method (entry 3).‡ The suspension method was very effective for the resolution of **1c** with **3**, whereas the recrystallization method gave poor results (entries 9 and 10). In the case of the resolution of **1d** with **3**, both methods are effective (entries 11 and 12). Neither the host **3** nor **5** forms an inclusion complex with **1e** which has a relatively bulky cyclohexyl group. However, (*R,R*)-(−)-*trans*-2,3-bis(hydroxydiphenylmethyl)-1,4-dioxaspiro[4,4]nonane **4**⁵ was useful for the resolution of **1e** by the recrystallization method.‡

5-Methoxydihydrofuranone **2** was also easily resolved by complexation with **5**. When a solution of **5** (2.0 g, 3.83 mmol) and racemic **2** (0.89 g, 7.67 mmol) in toluene–hexane (1 : 1; 20 ml) was kept at room temperature for 12 h, a 1 : 1 inclusion complex of **5** and (−)-**2** was obtained as colourless prisms (1.27 g, mp 119–120 °C) which upon heating *in vacuo* (220 °C 20 mmHg) gave (−)-**2** in 96% ee {0.223 g, 50% yield, [α]$_D$ −178 (*c* 0.47, MeOH)}.‡

The results of the resolution experiments (Table 1) suggest the necessity of a suitable host–guest combination to achieve optical chiral recognition. The best combination might depend on a delicate mutual relation between the host and guest which is not easy to predict. In a first attempt to clarify the

discriminative interactions, an X-ray analysis of the inclusion complex of **5** and **1a** was performed.§ The structure (Fig. 1) showed a single hydrogen bond between the host OH and the ester carbonyl of the guest as the only pertinent intermolecular interaction. It seems that resolution by the recrystallization and the suspension methods are complementary for the cases which produce relatively stable and unstable inclusion complexes respectively. Inclusion complexes formed by the crystallization experiments of entries 3, 7, 13 and 15 are stable and these can be further purified by recrystallization to provide optically pure compounds **1a**, **1b**, **1e** and **2** respectively. On the other hand, inclusion complexes of **3** and (+)-**1b**, **3** and (−)-**1c** and **3** and (+)-**1d** are too unstable to recrystallize. In these cases, the suspension experiment is the method of choice.

Footnotes

† All optical purities were determined by HPLC on the chiral solid phase Chiralpak AS (available from Daicel Chemical Industries Ltd, Himeji, Japan) using hexane–EtOH (95 : 5) as the eluent.

‡ The suspension method was not applicable to these combinations of host and guest (entries 2, 4, 8, 14 and 16).

§ *Crystal data* for 1 : 1 inclusion complex of **5** and **1a**, $C_{40}H_{44}O_7$, M_r = 636.79, colourless block-shaped crystal (0.48 × 0.50 × 0.52 mm), orthorhombic, space group $P2_12_12_1$, a = 8.476(1), b = 12.671(1), c = 31.566(8) Å, V = 3390.2(10) Å³, Z = 4, D_c = 1.248 g cm⁻³, $F(000)$ = 1360, $\mu(\text{Mo-K}\alpha)$ = 0.79 cm⁻¹. A total of 3782 independent reflections were measured (1.29° < θ < 26.0°, ω/2θ scan, Δω = 0.80 + 0.34 tanθ, T = 130 K, Mo-Kα radiation) on an Enraf-Nonius CAD-4F diffractometer. Of these reflections 3751 were unique. The intensity data were corrected for Lorentz and polarization effects and scale variations. The structure was solved by DIRDIF employing automated vector search rotation functions (ORIENT). All non-hydrogen positions could be located. The positional and anisotropic thermal displacement parameters for the non-hydrogen atoms were refined with block-diagonal least-squares procedures. Weights were introduced in the final refinement cycles. Refinement on *F* was carried out by full-matrix least-squares techniques; final *R* value 0.051, R_w = 0.051, S = 1.395 for 3029 observed reflections with $I \geqslant 2.5 \sigma (I)$, 556 parameters. Atomic coordinates, bond lengths and angles and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Information for Authors, Issue No. 1.

References

1 B. L. Feringa, B. de Lange, J. F. G. A. Jansen, J. C. de Jong, M. Lubben, W. S. Faber and E. P. Schudde, *Pure Appl. Chem.*, 1992, **64**, 1865; B. L. Feringa and J. C. de Jong, *Bull. Soc. Chim. Belg.*, 1992, **101**, 627.

2 M. T. Rispens, E. Keller, B. de Lange, R. W. J. Zijlstra and B. L. Feringa, *Tetrahedron Asymmetry*, 1994, **5**, 607.

3 F. Toda, *Top. Curr. Chem.*, 1987, **140**, 43; F. Toda, *Advances in Supramolecular Chemistry*, ed. G. W. Gokel, JAI Press, London, 1992, vol. 2, pp. 141–191; F. Toda, *Inclusion Compounds*, ed. J. L. Atwood, J. E. D. Davis and D. D. MacNicol, Oxford University Press, Oxford, 1991, vol. 4, pp. 126–187.

4 F. Toda and Y. Tohi, *J. Chem. Soc., Chem. Commun.*, 1993, 1238.

5 D. Seebach, A. K. Beck, R. Imwinkelried, S. Roggo and A. Wonnacott, *Helv. Chim. Acta*, 1987, **70**, 954; F. Toda and K. Tanaka, *Tetrahedron Lett.*, 1988, **29**, 551.