A diastereoselective route to 2,6-*syn*-disubstituted tetrahydropyrans: synthesis of the civet compound (+)-2-((2*S*,6*S*)-6-methyltetrahydro-2*H*-pyran-2-yl) acetic acid

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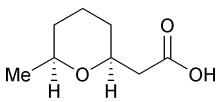
A diastereoselective synthesis of 2,6-*syn*-disubstituted tetrahydropyrans has been developed based on the ability of furanyl–ether chiral centres to epimerise readily under acidic conditions. This novel methodology was applied to the synthesis of (+)-2-((2*S*,6*S*)-6-methyltetrahydro-2*H*-pyran-2-yl) acetic acid, a component of the African civet cat's glandular marking secretion.

Many natural products of biological and pharmacological significance contain the 2,6-*syn* disubstituted tetrahydropyran moiety.[1] An example is (+)-2-((2*S*,6*S*)-6-methyltetrahydro-2*H*-pyran-2-yl) acetic acid (**1**), which was isolated by Maurer and coworkers in 1978 from civet—the perianal glandular pheromone secretion of the African civet cat (*Viverra civetta*).[2]



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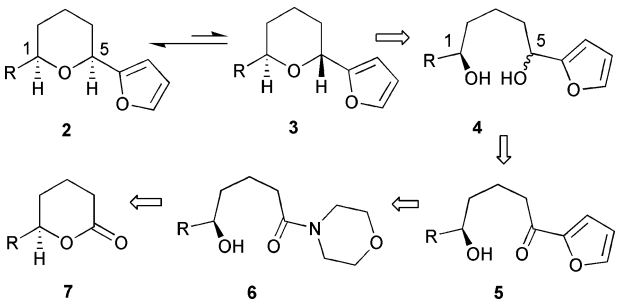
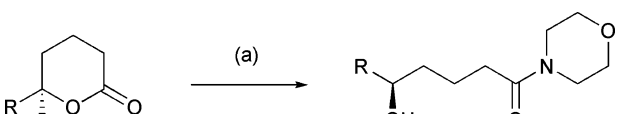
As both substituents in 2,6-*syn* disubstituted tetrahydropyrans are in equatorial positions, this configuration is thermodynamically favoured with respect to the 2,6-*anti*. Under conditions where one chiral centre readily epimerises, its configuration should be controlled by the other, configurationally more stable chiral centre. We have recently exploited the tendency of furanyl–ether chiral centres to epimerise under acidic conditions in a diastereoselective synthesis of 6,6-spiroketals[3] and we sought to extend this methodology to the tetrahydropyran system. Our plan is outlined retrosynthetically in Scheme 1.

The equilibrating mixture of *syn* and *anti* tetrahydropyrans **2** and **3** will result from the cyclisation of the configurationally stable secondary alcohol at C1 onto a cation formed at the C5 position of diol **4** under acidic conditions.[4] This cation formation (and the equilibration of **2** and **3**) will be facilitated by the electron donating ability of the adjacent furan group. Diol **4** will be formed as a mixture of C5 epimers by means of a non-selective reduction of the carbonyl group in **5**, which in turn will result from the coupling of a suitable furanyl–metal reagent with morpholine amide **6**.[5] Disconnection of this amide leads to the δ-valerolactones **7**, several of which are commercially available in racemic form.



Scheme 1 Retrosynthesis of 2,6-*syn* tetrahydropyrans.

Treatment of morpholine with aluminium chloride in dichloromethane followed by addition of the lactones **7a–e** afforded the corresponding morpholine amides **6a–e** in high yield (Scheme 2).[6] We initially decided to protect the secondary alcohol in **6a** as the trimethylsilyl ether (**8**) prior to furanylation (Scheme 3). Treatment of a tetrahydrofuran solution of furan with *n*-butyllithium at −10 °C followed by the addition of **8** led to furanyl ketone **9** in high yield. Exposure of **9** to a catalytic amount of hydrochloric acid in methanol at room temperature effected the smooth cleavage of the trimethylsilyl group (by TLC analysis). The reduction of the ketone group was carried out in the same pot by the addition of sodium borohydride to furnish the diol **4a** as an approximately 1 : 1 mixture of diastereomers (by NMR analysis). Although the overall yield of this sequence was acceptable, we decided to investigate a more direct approach, which avoided the protection step. Accordingly, amide **6a** was added to a solution of furanyl lithium. After the coupling was



(±) **7a-e**

	R	yield
6a	Me	95%
6b	C_5H_{11}	92%
6c	C_6H_{13}	89%
6d	C_7H_{15}	90%
6e	C_9H_{19}	98%

Scheme 2 *Reagents and conditions*: (a) morpholine, $AlCl_3$, DCM, −10 °C → rt, then **7**, DCM, −10 °C → rt.

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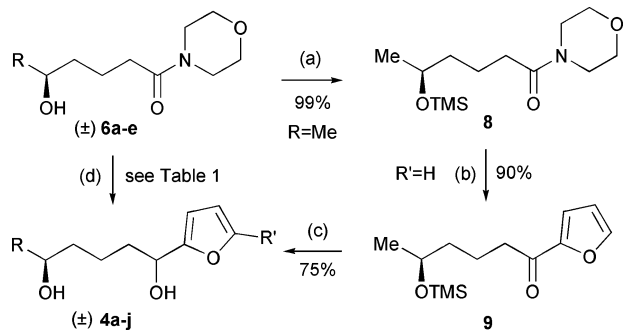


Scheme 3 *Reagents and conditions*: (a) TMSCl, imidazole, DCM, 0 °C; (b) *n*BuLi, furan, THF–hexanes, −10 °C, then **8**; (c) HCl (2N aq., cat.), MeOH, then $NaBH_4$; (d) *n*BuLi, furan or methylfuran, THF–hexanes, −10 °C, then **6a–e**, then MeOH, then $NaBH_4$, 0 °C.

Table 1 Results of one-pot diol formation

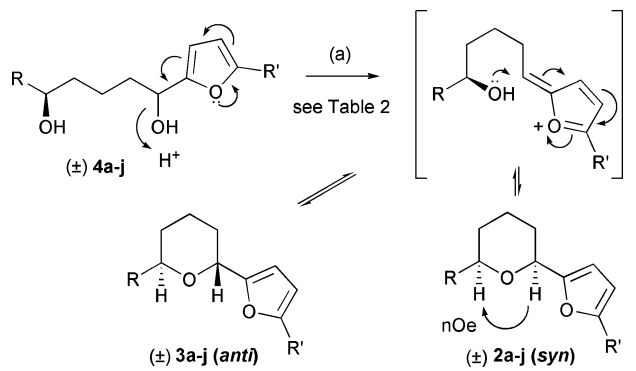
Entry	Amide	Diol	R	R′	Yield (%)[a]
1	**6a**	**4a**	Me	H	79
2	**6b**	**4b**	C_5H_{11}	H	88
3	**6c**	**4c**	C_6H_{13}	H	91
4	**6d**	**4d**	C_7H_{15}	H	88
5	**6e**	**4e**	C_9H_{19}	H	94
6	**6a**	**4f**	Me	Me	85
7	**6b**	**4g**	C_5H_{11}	Me	93
8	**6c**	**4h**	C_6H_{13}	Me	89
9	**6d**	**4i**	C_7H_{15}	Me	90
10	**6e**	**4j**	C_9H_{19}	Me	91

[a] Isolated yield after column chromatography over silica gel.

complete (by TLC analysis), the reaction was quenched with methanol. Subsequent addition of sodium borohydride afforded the desired diol **4a** in good yield (79%).

Using this direct one-pot approach, we synthesised ten different 1,5-diol substrates, coupling the amides **6a–e** to either furan or 2-methylfuran. All diols were formed as approximately 1 : 1 mixtures of diastereomers in high yield (Table 1).

With the substrates **4a–j** in hand, we turned our attention to the acid catalysed cyclisation–epimerisation. When the diols were taken up in deuterochloroform and exposed to catalytic amounts of *para*-toluenesulfonic acid, they rapidly cyclised to give a mixture of tetrahydropyrans (as monitored by TLC and/or NMR analysis), presumably by a mechanism similar to that shown in Scheme 4. The initial ratio of stereoisomers was



Scheme 4 *Reagents and conditions*: (a) *p*TSA, $CDCl_3$, rt, 7 d, then hexane, silica gel chromatography.

Table 2 Results of tetrahydropyran syntheses

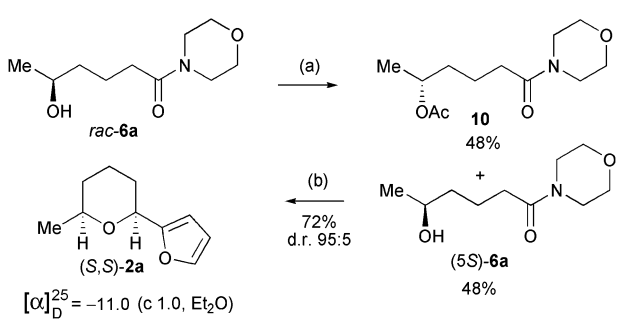
Entry	Diol	Product	R	R′	Yield (%)[a]	*syn–anti*
1	**4a**	**2a**	Me	H	90	95 : 5
2	**4b**	**2b**	C_5H_{11}	H	95	93 : 7
3	**4c**	**2c**	C_6H_{13}	H	91	94 : 6
4	**4d**	**2d**	C_7H_{15}	H	89	94 : 6
5	**4e**	**2e**	C_9H_{19}	H	93	94 : 6
6	**4f**	**2f**	Me	Me	92	95 : 5
7	**4g**	**2g**	C_5H_{11}	Me	90	93 : 7
8	**4h**	**2h**	C_6H_{13}	Me	88	91 : 9
9	**4i**	**2i**	C_7H_{15}	Me	94	94 : 6
10	**4j**	**2j**	C_9H_{19}	Me	90	94 : 6

[a] Isolated as a *syn–anti* mixture after column chromatography on silica gel.

approximately 2 : 1 in favour of the 2,6-*syn* tetrahydropyrans (stereochemistry determined by NOE) but equilibration led to an increase in the diastereomeric ratio. The reaction mixtures were monitored periodically by NMR analysis. After stirring at room temperature for 7 days, the diastereomeric ratios remained constant (d.r. greater than 10 : 1 in all cases, Table 2) and the reactions were worked up to afford products **2a–j** in high yield (Scheme 4, Table 2). Having established the diastereoselectivity of the tetrahydropyran formation, we commenced the synthesis of the civet cat secretion compound (+)-2-((2*S*,6*S*)-6-methyltetrahydro-2*H*-pyran-2-yl) acetic acid **1**. Racemic **6a** was exposed to an excess of vinyl acetate in toluene in the presence of catalytic *Candida antarctica* lipase B (CALB) supported on acrylic resin to afford a 1 : 1 mixture of the (5*R*)-acetate **10** and the (5*S*)-alcohol (5*S*)-**6a**, which were separated by column chromatography (Scheme 5).

The ee of (5*S*)-**6a** was determined to be at least 95% by comparison of the ^{1}H NMR spectra of its (*S*)-acetoxymandelate ester **11** (single set of peaks) with that of the (*S*)-acetoxymandelate esters (**11** and 5-*epi*-**11**) of *rac*-**6a** (two sets of peaks), Scheme 6. Inspection of these spectra also confirmed the 5*S* stereocentre.[7] Cyclisation to the tetrahydropyran (*S*,*S*)-**2a** was carried out in a likewise fashion to the racemate **2a** (Scheme 5). The furan group in (*S*,*S*)-**2a** was cleaved to the carboxylic acid **12** using sodium periodate and catalytic ruthenium trichloride (Scheme 7).[8]

Both (*R*) and (*S*) 1′-phenylethylamides (**16** and 1′-*epi*-**16**) of **12** were formed as single diastereoisomers with distinct ^{1}H NMR spectra, indicating that **12** was formed as a single



Scheme 5 *Reagents and conditions*: (a) *Candida antarctica* lipase B on acrylic resin, vinyl acetate, toluene, rt, 18 h; (b) i. *n*BuLi, furan, THF–hexanes, −10 °C, then (5*S*)-**6a**, then MeOH, then $NaBH_4$, 0 °C; ii. *p*TSA, $CDCl_3$, rt, 7 d, then hexane, silica gel chromatography.

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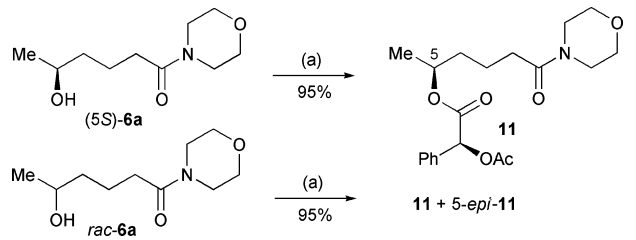
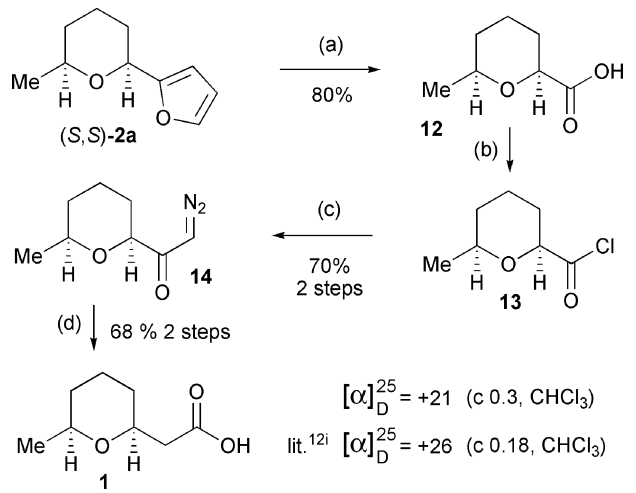
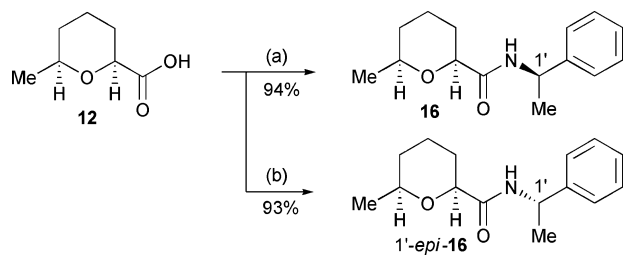


Scheme 6 *Reagents and conditions*: (a) (*S*)-acetylmandelic acid, EDCI, DMAP, DCM, rt.



Scheme 7 *Reagents and conditions*: (a) $RuCl_3 \cdot H_2O$ (cat.), $NaIO_4$, DCM, MeCN, H_2O; (b) oxalyl chloride, DMF (cat.), DCM or *N,N*-dimethyl(1-chloro-2-methyl-propenyl)amine; (c) $TMSCHN_2$, Et_3N, Et_2O, DCM; (d) AgOBz, Et_3N, MeOH, 80 °C, then NaOH, H_2O, 60 °C then HCl.



Scheme 8 *Reagents and conditions*: (a) (*R*)-1-phenylethylamine, EDCI, DMAP, DCM, 0 °C; (b) (*S*)-1-phenylethylamine, EDCI, DMAP, DCM, 0 °C.

enantiomer and proving that the stereochemical integrity of the (*S*)-methyl carbinol centre from (5*S*)-**6a** was still intact (Scheme 8).

Arndt–Eistert homologation began with the conversion of **12** to the corresponding acid chloride **13** (Scheme 7) using Ghosez's reagent.[9] Diazoketone formation was carried out without isolating **13** by the addition of triethylamine and trimethylsilyl-diazomethane to afford **14** in good yield. Wolff rearrangement[10] followed by saponification afforded the natural product **1**[11] whose spectral data and optical rotation were consistent with those reported in the literature.[2,12] Further exploration of the scope of this methodology is underway and will be published in due course.

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Notes and references

1 (*a*) G. Shi, J. F. Kozlowski, J. T. Schwedler, K. V. Wood, J. M. MacDougal and J. L. McLaughlin, *J. Org. Chem.*, 1996, **61**, 7988–7989; (*b*) D. E. Williams, M. Lapawa, X. D. Feng, T. Tarling, M. Roberge and R. J. Andersen, *Org. Lett.*, 2004, **6**, 2607–2610; (*c*) D. E. Williams, R. A. Keyzers, K. Warabi, K. Desjardine, J. L. Riffell, M. Roberge and R. J. Andersen, *J. Org. Chem.*, 2007, **72**, 9842–9845; (*d*) V. R. Hegde, M. S. Puar, P. Dai, M. Patel, V. P. Gullo, P. R. Das, R. W. Bond and A. T. McPhail, *Tetrahedron Lett.*, 2000, **41**, 1351–1354.

2 (*a*) B. Maurer and W. Thommen, *Helv. Chim. Acta*, 1979, **62**, 1096–1097; (*b*) B. Maurer, A. Grieder and W. Thommen, *Helv. Chim. Acta*, 1979, **62**, 44–47.

3 (*a*) S. Cahill, L. A. Evans and M. O'Brien, *Tetrahedron Lett.*, 2007, **48**, 5683–5686; (*b*) S. Cahill and M. O'Brien, *Tetrahedron Lett.*, 2006, **47**, 3665–3668.

4 (*a*) C. Galeffi, C. G. Casinovi and G. B. Marini-Bettolo, *Gazz. Chim. Ital.*, 1965, **95**, 95–100; (*b*) L. M. Harwood and J. Robertson, *Tetrahedron Lett.*, 1987, **28**, 5175–5176.

5 R. Martin, P. Romea, C. Tey, F. Urpi and J. Vilarrasa, *Synlett*, 1997, 1414–1416.

6 P. Lesimple and D. C. H. Bigg, *Synthesis*, 1991, 306–308.

7 (*a*) I. Chataigner, J. Lebreton, D. Durand, A. Guingant and J. Villieras, *Tetrahedron Lett.*, 1998, **39**, 1759–1762; (*b*) C. Spino and L. Weiler, *Tetrahedron Lett.*, 1987, **28**, 731–734.

8 P. H. J. Carlsen, T. Katsuki, V. S. Martin and K. B. Sharpless, *J. Org. Chem.*, 1981, **46**, 3936–3938.

9 A. Devos, J. Remion, A. M. Frisquehesbain, A. Colens and L. Ghosez, *J. Chem. Soc., Chem. Commun.*, 1979, 1180–1181.

10 M. S. Newman and P. F. Beal, *J. Am. Chem. Soc.*, 1950, 5163–5165.

11 The intermediates in this sequence were carried through as a 95 : 5 mixture of diastereomers. **1** was isolated as a single diastereomer after column chromatography on silica gel.

12 (*a*) M. F. Semmelhack and C. Bodurow, *J. Am. Chem. Soc.*, 1984, **106**, 1496–1498; (*b*) E. Keinan, K. K. Seth and R. Lamed, *J. Am. Chem. Soc.*, 1986, **108**, 3474–3480; (*c*) N. Greenspoon and E. Keinan, *J. Org. Chem.*, 1988, **53**, 3723–3731; (*d*) S. Hansson, J. F. Miller and L. S. Liebeskind, *J. Am. Chem. Soc.*, 1990, **112**, 9660–9661; (*e*) V. Ragoussis and V. Theodorou, *Synthesis*, 1993, 84–86; (*f*) H. Fujioka, H. Kitagawa, Y. Nagatomi and Y. Kita, *J. Org. Chem.*, 1996, **61**, 7309–7315; (*g*) M. G. Banwell, B. D. Bissett, C. T. Bui, H. T. T. Pham and G. W. Simpson, *Aust. J. Chem.*, 1998, **51**, 9–18; (*h*) D. J. Dixon, S. V. Ley and E. W. Tate, *J. Chem. Soc., Perkin Trans. 1*, 2000, 2385–2394; (*i*) M. C. Carreno, R. Des Mazery, A. Urbano, F. Colobert and G. Solladie, *J. Org. Chem.*, 2003, **68**, 7779–7787; (*j*) R. J. Hinkle, Y. J. Lian, N. D. Litvinas, A. T. Jenkins and D. C. Burnette, *Tetrahedron*, 2005, **61**, 11679–11685; (*k*) S. Mori, S. Iwamoto and S. Yamauchi, *Biosci., Biotechnol., Biochem.*, 2006, **70**, 712–717.