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

Matthew O'Brien,*^a Shane Cahill^b and Lyndsay A. Evans^b

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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-((2S,6S)-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-((2S,6S)-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



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-spiroketals³ 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



Scheme 1 Retrosynthesis of 2,6-syn tetrahydropyrans.

amide leads to the δ -valerolactones 7, several of which are commercially available in racemic form.

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



Scheme 2 Reagents and conditions: (a) morpholine, AlCl₃, DCM, $-10 \ ^{\circ}C \rightarrow rt$, then 7, DCM, $-10 \ ^{\circ}C \rightarrow rt$.

^a Whiffen Laboratory, University Chemical Laboratory, Cambridge University, Lensfield Road, Cambridge, UK CB2 1EW.

E-mail: mo263@cam.ac.uk

^b School of Chemistry, Trinity College Dublin, College Green, Dublin, D2, Republic of Ireland



Scheme 3 Reagents and conditions: (a) TMSCl, imidazole, DCM, $0 \,^{\circ}C$; (b) *n*BuLi, furan, THF-hexanes, $-10 \,^{\circ}C$, then **8**; (c) HCl (2N aq., cat.), MeOH, then NaBH₄; (d) *n*BuLi, furan or methylfuran, THF-hexanes, $-10 \,^{\circ}C$, then **6a-e**, then MeOH, then NaBH₄, $0 \,^{\circ}C$.

Table 1 Results of one-pot diol formation

| Entry | Amide | Diol | R | \mathbf{R}' | Yield (%) ^a |
|-----------------------|-----------------|------------|---------------|---------------|------------------------|
| 1 | 6a | 4a | Me | Н | 79 |
| 2 | 6b | 4b | $C_{5}H_{11}$ | Н | 88 |
| 3 | 6c | 4c | C_6H_{13} | Н | 91 |
| 4 | 6d | 4d | C_7H_{15} | Н | 88 |
| 5 | 6e | 4 e | $C_{9}H_{19}$ | Н | 94 |
| 6 | 6a | 4 f | Me | Me | 85 |
| 7 | 6b | 4g | $C_{5}H_{11}$ | Me | 93 |
| 8 | 6c | 4h | $C_{6}H_{13}$ | Me | 89 |
| 9 | 6d | 4i | $C_{7}H_{15}$ | Me | 90 |
| 10 | 6e | 4j | $C_{9}H_{19}$ | Me | 91 |
| ^a Isolated | d yield after c | olumn chr | omatography | y over silie | ca 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

 Table 2
 Results of tetrahydropyran syntheses

| Entry | Diol | Product | R | \mathbf{R}' | Yield (%) ^a | syn–anti |
|----------------------|------------|-------------------|---------------|---------------|------------------------|-----------|
| 1 | 4a | 2a | Me | Н | 90 | 95:5 |
| 2 | 4b | 2b | $C_{5}H_{11}$ | Н | 95 | 93:7 |
| 3 | 4c | 2c | C_6H_{13} | Н | 91 | 94:6 |
| 4 | 4d | 2d | C_7H_{15} | Н | 89 | 94:6 |
| 5 | 4 e | 2e | C_9H_{19} | Н | 93 | 94:6 |
| 6 | 4f | 2f | Me | Me | 92 | 95:5 |
| 7 | 4g | 2g | $C_{5}H_{11}$ | Me | 90 | 93:7 |
| 8 | 4ĥ | 2h | $C_{6}H_{13}$ | Me | 88 | 91:9 |
| 9 | 4 i | 2i | C_7H_{15} | Me | 94 | 94:6 |
| 10 | 4j | 2j | C_9H_{19} | Me | 90 | 94:6 |
| ^a Isolate | ed as a | <i>syn–anti</i> m | ixture afte | er colu | mn chromatog | graphy 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-((2S,6S)-6-methyltetrahydro-2H-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 (5R)-acetate 10 and the (5S)-alcohol (5S)-6a, which were separated by column chromatography (Scheme 5).

The ee of (5S)-**6a** was determined to be at least 95% by comparison of the ¹H 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 ¹H NMR spectra, indicating that 12 was formed as a single



Scheme 4 *Reagents and conditions:* (a) *p*TSA, CDCl₃, rt, 7 d, then hexane, silica gel chromatography.





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 NaBH₄, 0 °C; ii. *p*TSA, CDCl₃, rt, 7 d, then hexane, silica gel chromatography.



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) TMSCHN₂, Et₃N, Et₂O, DCM; (d) AgOBz, Et₃N, MeOH, 80 °C, then NaOH, H₂O, 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 (5S)-**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 rearrangement¹⁰ 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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