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A Simple Asymmetric Synthesis of Cis-2,6-Disubstituted Tetrahydropyran Acetic Acid Derivatives

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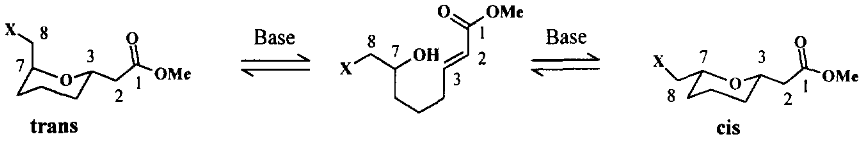
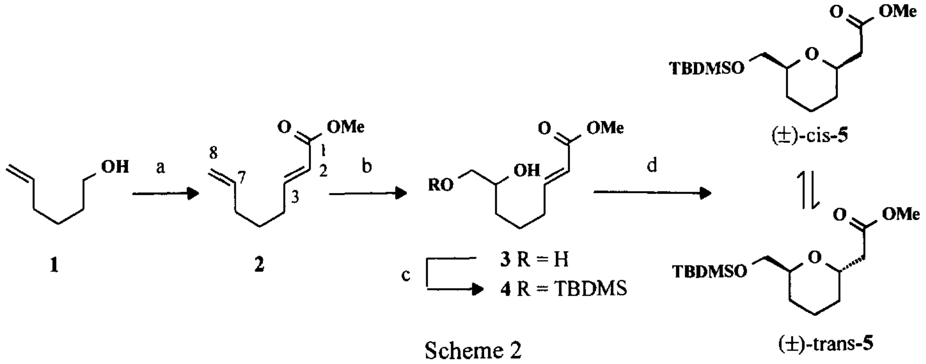
Abstract: A new asymmetric synthesis of functionalised cis-2,6-disubstituted tetrahydropyran acetic acids is described. The utility of the procedure is illustrated by the synthesis of (+) and (-)-(cis-6-methyltetrahydropyran-2-yl)acetic acid, a glandular secretion of the civet cat (*Viverra civetta*). © 1997, Elsevier Science Ltd. All rights reserved.

Many natural products contain the 2,6-disubstituted tetrahydropyran ring system, and as a result they have been the target of numerous synthetic studies.[1] Conceptually one of the most simple routes to this compound class is an intramolecular Michael addition of the type shown in Scheme 1. An advantage of this approach is that the reaction is thermodynamically controlled, and formation of the cis-substituted tetrahydropyran (with both substituents equatorial) becomes almost the exclusive product when the reaction reaches equilibrium.[2]



Scheme 1

It therefore follows that the chirality at C3 will be induced by the chirality of the secondary alcohol moiety at C7. Surprisingly, there have been relatively few asymmetric syntheses for such functionalised tetrahydropyrans based on this approach.[3] We envisaged that such molecules would be available in high enantiomeric purity *via* Sharpless asymmetric dihydroxylation (ADH) of a terminal olefin tethered to an acrylate functionality, and subsequent intramolecular Michael addition. To test this hypothesis we first synthesised the racemic compound (Scheme 2).



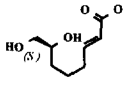
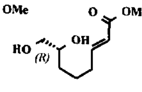
Scheme 2

a) DMSO/$(COCl)_2$/CH_2Cl_2, -78°C, then Et_3N, -78°C to rt, then add $Ph_3P{=}CHCO_2Me$, rt (94%). b) NMO/acetone/H_2O, 0°C to rt (59%) c) TBDMSCl/imidazole/CH_2Cl_2, rt (96%). d) NaH/THF, rt (93%).

Commercially available 5-hexen-1-ol **1** was subjected to Swern oxidation[4] and the resultant volatile aldehyde not isolated but converted *in situ* to the α,β-unsaturated ester **2** in 94% distilled yield (bp 82-85°C, 16mmHg).[5] The key hydroxylation was first carried out using standard catalytic osmium tetroxide conditions.[6] Regioselective oxidation occurred at the terminal double bond and the 7,8-diol **3** could be obtained in 59% yield after flash chromatography.[7] The diol **3** was then selectively protected at the primary functionality with the bulky TBDMS group setting the stage for the key intramolecular Michael addition. Treatment of **4** with NaH (1.5eq.) in THF at room temperature led very quickly to a *ca.* 1:1 mixture of the cis and trans 2,6-disubstituted tetrahydropyrans **5** as shown by TLC and GC analysis. After allowing to stir at room temperature for 3h, thermodynamic equilibrium was reached which showed a ratio of cis:trans **5** of 97:3 (GC analysis).

Having shown the synthesis feasable, we next turned our attention to the asymmetric version of the reaction. Sharpless asymmetric dihydroxylation[8] of the precursor **2** was investigated using 3eq. of potassium hexaferrocyanate(III), 3eq. of potassium carbonate, and 0.01eq of potassium osmate(VI)dihydrate in a 1:1 mixture of t-BuOH:H_2O at 0.1 M substrate concentrations, and varying the catalyst and temperature (Table 1).

Table 1. Asymmetric Dihydroxylation of **2**

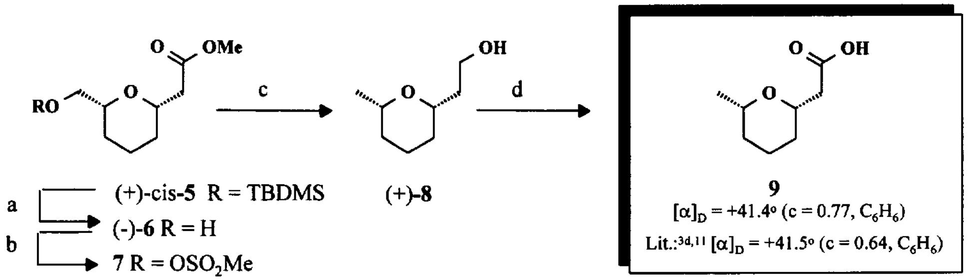
Entry	Catalyst	Temperature (°C)	Regioselectivity	Yield of **3** (%)	Enantiomeric Ratio 	
1	$(DHQD)_2PTHAL$	0 to rt	4:1	49	3	97
2	$(DHQ)_2PTHAL$	0 to rt	4:1	49	91	9
3	$(DHQD)_2PTHAL$	0	4:1	46	10	90
4	$(DHQ)_2PTHAL$	0	4:1	49	80	20
5	$(DHQD)_2PYR$	0 to rt	49:1	54	5	95
6	$(DHQ)_2PYR$	0 to rt	15:1	49	88	12

$(DHQD)_2$ = Dihydroquinidine, $(DHQ)_2$ = Dihydroquinine.

The enantiomeric ratios of the product **3** obtained were determined by ^1H NMR of the bis-Mosher esters.[9] The stereochemistry of the products is predicted from the mnemonic reported by Sharpless.[8a] The yields in Table 1 refer to isolated compound after flash chromatography, and although the yields are only fair, the compounds are readily separable,[7] and we routinely carried out the reaction on a 0.1 mole scale. The regioselectivity of diol formation (oxidation at C7-C8 verses C2-C3) was assessed by GC analysis of the product mixture obtained after work-up, and in all reactions, no more than 10% of tetrahydroxylated compound was isolated.[7]

From the results in Table 1, several points are noteworthy: Carrying out the reaction at the lower temperature leads to less enantioselective oxidation (entries 1 and 3, and 2 and 4). The pyrimidine ligands do not perform as well as the phthalazine ligands with regard to enantioselectivity. With both the pyrimidine and phthalazine ligands, the dihydroquinidines (i.e $(DHQD)_2PTHAL$[8b] and PYR[8c] gave slightly better enantiomeric product ratios than the pseudoenantiomers $(DHQ)_2PTHAL$[8b] and PYR[8c] under all conditions studied.[10] Interestingly, the phthalazine ligands enabled more 2,3-diol to be isolated than the pyrimidine ligands (compare entries 1-4 with 5 and 6).

The product (+)-**3** ($[\alpha]_D$ = +2.5° (c = 0.59, $CHCl_3$)) obtained according to entry 1 in Table 1, was converted to the protected tetrahydropyran derivative (+)-cis-**5** ($[\alpha]_D$ = +10.1°(c = 1.07, $CHCl_3$)), as shown in Scheme 2. To illustrate the usefulness of this synthesis, and to confirm the stereochemistry predicted from the Sharpless mnemonic for asymmetric dihydroxylation, (+)-cis-**5** was further converted to the perfume component of the civet cat (*Viverra civetta*)[11] as shown in Scheme 3.[12]

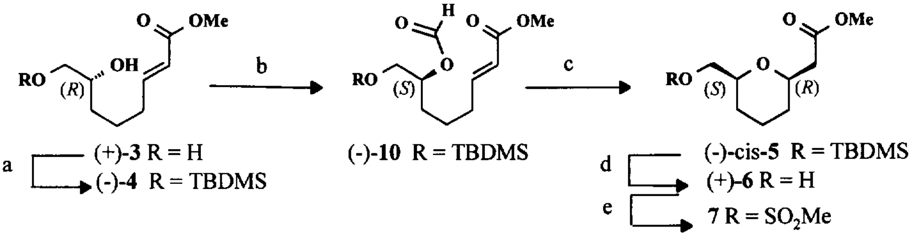


Scheme 3

a) HF (4% aq)/CH_3CN, rt (97%). b) $MeSO_2Cl/Et_3N$/DMAP(cat.)/CH_2Cl_2, 0°C to rt (94%). c) $LiAlH_4/Et_2O$, rt (84%). d) CrO_3/acetone, rt (93 %).

Comparison of the optical rotation values for the sample obtained with those reported in the literature[3d,11] for the natural product confirmed the absolute stereochemistry of (+)-**9** to be (*S*,*S*), which requires that the Sharpless dihydroxylation with $(DHQD)_2PTHAL$ indeed leads to diol (+)-**3** with (*R*) configuration at the newly created asymmetric centre.

To obtain the antipode of (+)-**9** in optical purity higher than that achievable by ADH (as shown in Table 1, the pseudoenantiomer ($(DHQ)_2PTHAL$ leads only to 91:9 ratio of enantiomers) a part of the synthesis was slightly modified (Scheme 4).



Scheme 4

a) TBDMSCl/imidazole/CH_2Cl_2, rt (96%). b) Ph_3P/DEAD/HCO_2H/THF, 0°C to rt (94%). c) NaOMe/MeOH/rt (72%). d) HF(4% aq)/CH_3CN, rt (95%). e) $MeSO_2Cl/Et_3N$/DMAP(cat.)/CH_2Cl_2, 0°C to rt (92%).

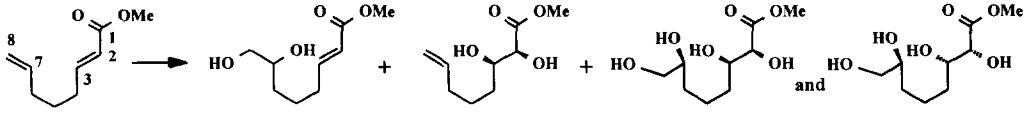
The key steps in the modified synthesis were a Mitsunobu reaction[13] which gave the required inversion, and direct cyclisation of the resultant formyl ester (-)-**10** ($[\alpha]_D$ = -8.0° (c = 1.02, $CHCl_3$)), to (-)-cis-**5** ($[\alpha]_D$ = -10.9° (c = 1.10, $CHCl_3$)). This latter reaction was accomplished using NaOMe in MeOH at room temperature. Under these conditions, equilibrium is reached more slowly (7 days), and the ratio of cis:trans **5** is only 9:1, which accounts for the lower yield of isolated (-)-cis **5**. Alternatively, the reaction can be terminated after consumption of starting material (6 h) and the mixture of cis and trans isomers converted to the equilibrium ratio (97% cis-**5**) using NaH in THF as shown in Scheme 1. Conversion of (-)-cis-**5** to (-)-**9** ($[\alpha]_D$ = -42.1 (c = 0.82, C_6H_6)) was then carried out according to Scheme 3.

The intermediates (+)- and (-)-**7** are particularly useful for preparing more highly functionalised derivatives, and applications of this will be reported shortly.

ACKNOWLEDGEMENT: The authors acknowledge the skillful technical contributions of Ms. G. Arnold.

REFERENCES AND NOTES

1. Boivin, T. L. B. *Tetrahedron*, 43, 3309, **1987** and references cited therein.
2. A recent publication has appeared on the role of double bond geometry in controlling the diastereoselectivity of this type of cyclisation. See, Banwell, M.G.; Bui. C.T.; Pham, Ha-T. T.; Simpson, G.W. *J. Chem. Soc. Perkin Trans. I*, , **1996**, 967.
3. For the first example of this type of strategy see a) Seebach, D.; Pohmaktor, M.S. *Helv. Chim. Acta*, **1979**, *62*, 1096. For other examples see b) Kocienski, P. J.; Smith, N. D.; Street, S. D. A. *Synthesis*, **1996**, 652. c) Banwell, M. G.; Bui, C. T.; Simpson G. W.; Watson, K.G. *Chem. Commun*., **1996**, 723. d) Machinaga, N.; Kibayashi, C. *Tetrahedron Lett*., **1993**, *34*, 5739. e) Palazon, J. M.; Soler, M. A.; Ramirez, M. A.; Martin, S.V. *Tetrahedron Lett*, **1993**, *34*, 5467. Intramolecular 1,4-addition of oxyanions to tethered chiral α,β-unsaturated sulfoxides has been used as an approach to prepare 2,6-disubstituted tetrahydropyrans in a diastereoselective manner. See; f) Mandai, T.; Ueda, M.; Kashiwagi., K.; Kawada, M.; Tsuji, J. *Tetrahedron Lett*., **1993**, *34*, 111.
4. Mancuso, J.A.; Swern, D. *Synthesis*, **1981**, 165.
5. ^{1}H NMR and GC/MS showed a ratio of ≥ 95:5 of E:Z isomers.
6. Van Rheenen, V.; Kelly, R.C.; Cha, D.Y. *Tetrahedron Lett*, **1976**, 1973.
7. This oxidation leads to the products shown below.:



2 **7,8-Diol** **Racemic-cis-2,3-Diol** **Racemic-2,3,7,8-Tetrol**

   The 7,8-diol and 2,3-diol are readily separated by flash chromatography. The 1:1 mixture of diastereoisomeric tetrols were isolated by concentration of the water phase obtained after normal aqueous work-up and extraction of the residue. *7,8-Diol* (**3**):^{1}H NMR (300 MHz, $CDCl_3$:CD_3OD, 9:1): 1.22-1.61 (*m*, 4H); 2.145 (*qt*, J = 7.2, 1.5 Hz, 2H); 3.27 (*dd*, J = 11.1, 7.2 Hz, 1H); 3.44 (*dd*, J = 11.1, 3.3 Hz, 1H); 3.52 (*m*, 1H); 3.61 (*s*, 3H); 5.72 (*dt*, J = 15.7, 1.5 Hz, 1H); 6.85 ppm (*dt*, J = 15.7, 7.2 Hz). ^{13}C NMR (75.4 Mhz, $CDCl_3$): 23.71; 31.77; 32.07; 51.28; 66.32; 71.69; 120.93; 149.37; 167.31 ppm.

   2,3-Diol: ^{1}H NMR ($CDCl_3$): 1.39-1.65 (*m*, 4H); 2.09 (*qt*, J = 6.6, 1.5 Hz, 2H); 3.17 (*br s*, 2H); 3.81 (*s*, 3H); 3.87 (*m*, 1H); 4.09 (*dd*, J = 6.0, 2.1 Hz, 1H); 4.96 (*br d*, J = 10.2 Hz, 1H); 4.99 (*dq*, J = 18.5, 1.5 Hz, 1H); 5.79 ppm (*ddt*, J = 18.5, 10.2, 6.6 Hz, 1H). ^{13}C NMR ($CDCl_3$): 24.72; 32.25; 32.62; 52.51; 72.33; 73.28; 114.70; 138.36; 174.10 ppm.

   2,3,7,8-Tetrol. ^{1}H NMR (CD_3OD): 1.08-1.71 (*m*, 6H); 3.31-3.82 (*m*, 5H); 3.74ppm (*s*, 3H). ^{13}C NMR (CD_3OD) 22.83; 33.98; 34.03; 34.06; 34.11; 52.53; 67.25; 73.02; 73.06; 73.53; 74.76; 74.80; 175.27 ppm.
8. a) Kolb, H.C.; Van Nieuwenhze, M.S.; Sharpless, K.B. *Chem.Rev*., 1994, 94, 2483. b) Sharpless K.B.; Amberg, W.; Bennani, Y.L.; Crispino, G.; Harrtung, J.; Jeong, K.-S.; Kwong, H.-L.; Morikawa, K.; Wang, Z.-M.; Xn, D.; Zhang, X.-L. *J.Org.Chem*., **1992**, *57*, 2678. c). Crispino, G.; Jeong, K.-S.; Kolb, H.C.; Wang, Z.-M.; Xn, D.; Sharpless, K. B. *J.Org.Chem*., **1993**, *58*, 3785.
9. The bis-Mosher esters were synthesised from freshly prepared (*S*)-(+)-MTPA-Cl (2.2eq.) and DMAP (3eq.) in CH_2Cl_2. ^{1}H NMR analysis of the racemic sample showed signals for the β-olefinic protons (*dt*, J = 15.6, 1.5 Hz) at 5.808 (*t*), 5.758 (*q*) and 5.715 ppm (*t*). The enantiomer ratios were thus determined by integration of the triplets at 5.808 and 5.715 ppm in the non-racemic samples.
10. This phenomenon is usually observed. See reference 8a.
11. Maurer, B.; Grieder, A.; Thommen, W. *Helv. Chim. Acta*, **1979**, *62*, 44. For syntheses see: Ragoussis, V.; Theodorou, V. *Synthesis*, **1993**, 84 and references cited therein.
12. The conversion **6** to **9** is analogous to that reported by: Jones, J.B.; Hinks, R.S. *Can. J. Chem*., **1987**, *65*, 704.
13. Mitsunobu, O. *Synthesis*, **1981**, 1.

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