Tetrahedron Vol 47, No 35, pp 7357-7362, 1991
Printed in Great Britain

0040-4020/91 $3 00+ 00
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Asymmetric Hydrogenation of 3-Methyl-Fumaric and Maleic Ester Monoaldehydes Protected as Neph-Derived Oxazolidines

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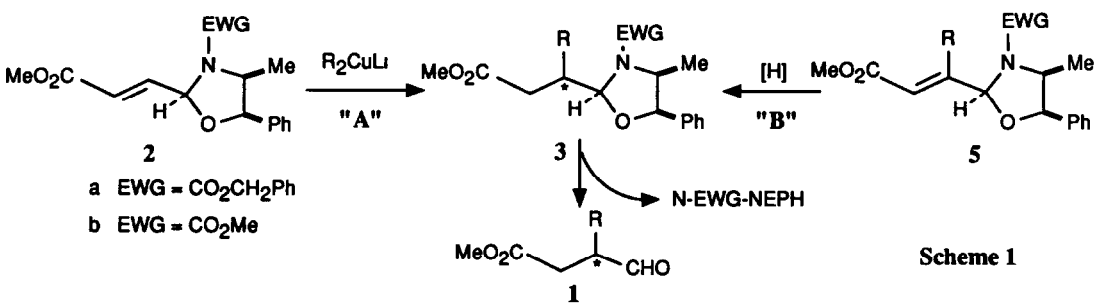
(*Received in UK* 23 *May* 1991)

Keywords *Asymmetric hydrogenation, oxazolidines, C-4 synthons*

Abstract *The hydrogenation of 3-methyl-fumaric and maleic ester mono aldehydes protected as oxazolidines of nor-ephedrine (NEPH) derivation has been studied This transformation takes place with moderate to good π-face stereodifferentiation and allows the preparation of non-racemic 3-methyl-succinaldehydic acid methyl ester (1, R=Me) The factors dictating the diastereocontrol are discussed*

The preparation of non-racemic C-4 synthons and their use as building blocks in the synthesis of more complex molecules of biological interest is a subject of current interest [1]

We recently reported that 3-alkyl substituted succinic aldehydes **1** could be obtained in high enantiomeric excess via *Si*-face organocuprate conjugate addition to acrylate **2** followed by non-destructive removal of the chiral auxiliary (Scheme 1, route A) [2]

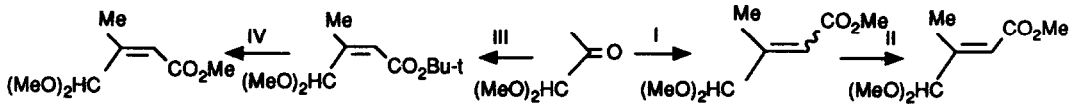


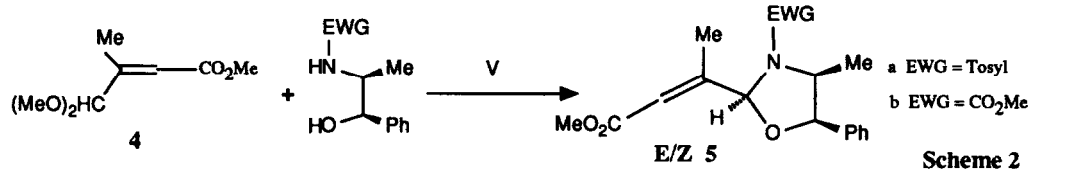
Scheme 1

In our continuing interest in this field we have now developed a "hydrogenative" route to 3, i.e. a synthetic pathway in which the transferred moiety and a resident group β to the carbonyl ester were formally exchanged with respect to the original sequence (Scheme 1, route B) [3]

Acetals **4E** and **4Z** were easily synthesized *via* olefination of pyruvaldehyde dimethyl acetal. Horner-Emmons[4] condensation using trimethylphosphonoacetate followed by double bond equilibration under acidic conditions gave virtually pure **4E**. Enriched **4Z** was best obtained through Petersen condensation of t-butyl trimethylsilylacetate[5] followed by t-butyl-to-methyl ester exchange. Cyclization between **4** and the N-protected nor-ephedrines N-CO_2Me-NEPH and N-Ts-NEPH took place smoothly under BF_3Et_2O

catalysis affording the *cis* alkenyl-oxazolidines **5** in high yields and with E Z ratios reflecting those of the acetal precursors (Scheme 2)



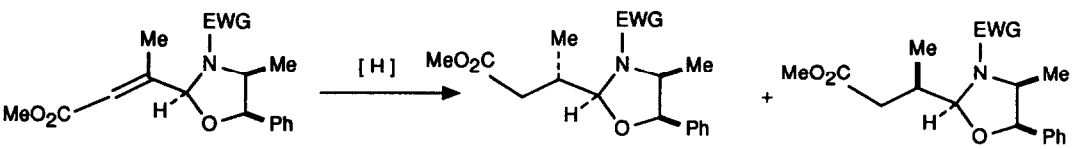


Scheme 2

I NaH, THF, $MeO_2CCH_2PO(OMe)_2$ 0-25 C, (90%), II a) PTSOH, Et_2O/H_2O, R T (60%), b) $HC(OMe)_3$, NH_4NO_3, MeOH, (80%), III LDA, TMS-CH_2CO_2Bu-t, 0 C, (98%), IV a) KOH, EtOH, 65 C, b) MeI, MeCN (40%) V BF_3Et_2O, CH_2Cl_2, 25 C, (EWG=CO_2Me 85%, EWG = Ts 90%)

Hydrogenation of **5** E/Z was performed using the following systems *a*) H_2(1 atm)/10% Pd/C/MeOH,[6] *b*) $NaBH_4/CoCl_2$/MeOH[7] and *c*) $SmI_2/THF/H_2O$[8] and the results are shown in scheme 3 Methods *a* and *b* always favoured the 2'R diastereoisomer regardless of the starting double bond geometry However, in the N-Ts series the Z isomer behaved better than the corresponding E in terms of selectivity On the other hand, the SmI_2 promoted reduction of **5b** gave a high π-face selection in favour of the opposite diastereoisomer although in a rather low yield [9]

Scheme 3 Asymmetric hydrogenation of adducts **5a** and **5b**



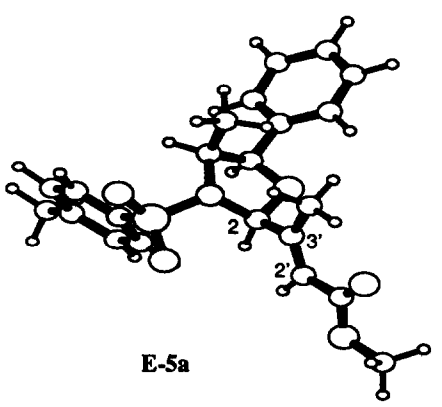
Entry	EWG	E Z	[H]	Solv	2'R/2'S	yield%	Method
1	Ts	95 5	H_2, Pd/C	MeOH	83 17	97	A
2	Ts	95 5	$NaBH_4/CoCl_2$	MeOH	80 20	75	B
3	Ts	5 95	H_2, Pd/C	MeOH	95 5	70	A
4	Ts	5:95	$NaBH_4/CoCl_2$	MeOH	95 5	75	B
5	CO_2Me	98 2	H_2, Pd/C	MeOH	88 12	81	A
6	CO_2Me	30 70	H_2, Pd/C	MeOH	88 12	80	A
7	CO_2Me	88 12	$NaBH_4/CoCl_2$	MeOH	70 30	54	B
8	CO_2Me	88 12	SmI_2	THF/H_2O	10 90	35	C

Subsequent standard cleavage of adducts **3** from entries 3 and 5 (scheme 3) gave aldehyde **1** in enantiomeric purities corresponding to the d r of the starting adducts [14]

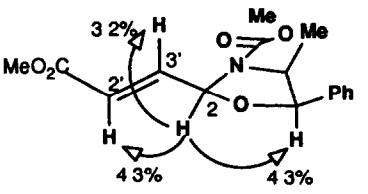
Inspection of the results presented in scheme 3 reveals that hydrogenations with methods *a* and *b* take place with topicity opposite to the corresponding organocuprate addition In this respect, the degree of substitution of the starting alkenes as well as the nature of the reacting systems in the two methods are likely to be determinant for the topicity inversion In fact, alkene **2b**, known to stereoselectively react with alkylcuprates, undergo virtually random deuterium incorporation upon catalytic deuteration (D_2, Pd/C, MeOH) or treatment with $NaBD_4/CoCl_2$ (isotopic ratios 60 40 and 50 50 respectively).

The X-ray crystal structure of the N-tosyl derivative **5a** (see fig. 1) shows eclipsing between H-2 and $C_{2'}$-$C_{3'}$ bond, a disposition already found in the solid state conformation of its nor-derivative **2** (EWG=Ts) [2] However, N O E difference experiments on the N-CO_2Me derivatives **E-2b** and **E-5b**, indicated that in solution this conformational bias is maintained only by the latter alkene Irradiation of H_{C2} in **E-2b** caused sizable Overhauser effects of comparable magnitude on both $H_{C2'}$ and H_{C3} The same experiment on **E-5b** gave rise to N.O E signals only for $H_{C2'}$ the methyl group on $C_{3'}$ remaining unaffected These data are suggestive of a pronounced preference for the eclipsed H-2/$C_{2'}$-$C_{3'}$ disposition of the trisubstituted alkene as opposed to a broader conformational freedom of the disubstituted alkenyl fragment in **E-2b**

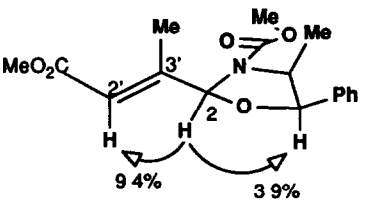
Fig 1. Left X-ray crystal structure of E-5a Right Relevant N O E signals in E-2b and E-5b



E-5a



E-2b



E-5b

Assuming that the reactive conformations in these hydrogenations are close to that highly favoured in the ground state, diastereocontrol appears to be governed by preferred H-transfer from the metal surface to the complexed olefin on the side of space occupied by the ring oxygen, a result in agreement with a π-face selectivity of steric nature

In summary, the hydrogenation of 3-methyl-fumaric and maleic ester mono-aldehydes protected as N-EWG oxazolidines is a useful method towards enantiomerically enriched methyl succinic derivatives Although the degree of π-face differentiation is somewhat lower in comparison to the cuprate approach, the simplicity of experimental execution (no anhydrous conditions required, room temperature reactions) as well as the easy access to the alkenyl precursors make this new method a valid alternative to the previously described cuprate approach

Scope and mechanism of the samarium-based double bond reduction are presently under investigation [15]

Experimental

^{1}H-NMR spectra were recorded with a Bruker AC-200 or WP-80 or Varian EM-60, while ^{13}C-NMR spectra were recorded with a Bruker AC-200 instrument in the FT mode with tetramethylsilane as internal standard and using $CDCl_3$ as the solvent unless otherwise stated. IR spectra were recorded with a Perkin-Elmer 457 spectrophotometer. Silica gel 60 F_{254} plates (Merck) were used for analytical TLC, 270-400 mesh silica gel (Merck) for flash chromatography "Dry" solvents were distilled under N_2 just before use: tetrahydrofuran (THF) was distilled from sodium metal in the presence of benzophenon All reactions employing dry solvents were run under a nitrogen (from liquid N_2) atmosphere Melting points are uncorrected. All new stable compounds gave satisfactory elemental analysis (C ±0 3%; H ±0.2%; N ±0 2%)

Methyl 4,4-dimethoxy-3-methyl-2-butenoate:
(65 35 E:Z mixture)·
To a suspension of 80% NaH (837 mg, 27.9 mmol) in THF (140 ml), trimethylphosphonoacetate (4 622 g, 25 38 mmol) dissolved in THF (20 ml) was added dropwise at 0°C in 10 min. After 30 min stirring at this temperature (H_2 evolution was completely ceased) pyruvaldehyde dimethyl acetal (3 ml, 25 38 mmol) in THF (5 ml) was added and stirring was continued for 1h at 0°C Treatment with sat aqueous NH_4Cl and subsequent extractive work-up gave the crude product Bulb-to-bulb distillation (140-150 °C pot temp , 16 mmHg) afforded the pure ester (90% yield)

(>98 2 E·Z mixture)·
The dimethylacetal 4 (65:35 E Z mixture, 3 8g, 21.83 mmol) was added to Et_2O (22 ml), H_2O (10 ml) and p-toluenesulphonic acid (1g, 5.26 mmol) and the resulting biphasic system was vigorously stirred at r t for 6h. After separation of the ethereal layer and repeated extractions of the aqueous phase with Et_2O, the collected organic layers where washed with sat $NaHCO_3$ and brine. Na_2SO_4 drying followed by solvent evaporation gave the crude aldehyde which was bulb-to-bulb distilled (100 °C pot temp , 16 mmHg) ^{1}H-NMR ($CDCl_3$, 60 MHz)· δ 2 05 (3H, d, J=3 6 Hz), 3 75 (3H, s), 6 48 (1H, m), 9 55 (1H, s)
Methyl orthoformate (1 4 ml, 13.1 mmol) was added to the aldehyde followed by a 1.2 M solution of NH_4NO_3 (43.2 mg, 0.54 mmol) in MeOH (0 45 ml) After 20 min refluxing (complete consumption of the aldehyde by TLC) the mixture was allowed to reach r t , diluted with Et_2O (5ml) and then filtered through a Buckner funnel 1 M aqueous NH_3 was then added until the organic phase became clear. Washing with H_2O followed by K_2CO_3 drying gave the crude dimethyl acetal wich was bulb-to-bulb distilled (140-150 °C pot temp , 16 mmHg) (48% yield from the dimethyl acetal). ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 2.13 (3H, d, J=1 2 Hz), 3 32 (6H, s), 3.75 (3H, s), 4 62 (1H, s), 6 05 (1H, m)

(30 70 E Z mixture):
t-Butyl 4,4-dimethoxy-3-methyl-2-butenoate[5] (192 mg, 0 89 mmol), 85% KOH (63 6 mg, 1.33 mmol) and 95% EtOH (1ml) were heated at 65 °C for 12 h The solvent was evaporated and the resulting residue was suspended in CH_3CN (22 2 ml) Methyl iodide (50 4 mg, 3 35 mmol) and Bu_4NHSO_4 (75 mg, 0 22 mmol) were added and the reaction mixture was stirred at room temperature for 10 min The solvent was removed under vacuum, and the residue diluted with H_2O and extracted with Et_2O The organic extracts were dried over Na_2SO_4, filtered, the solvent evaporated and the residue purified by flash chromatography (pentane/Et_2O 80/20) to give 61 8 mg of 4 (40% yield) 4-Z ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 1 89 (3H, d, J=1 5 Hz), 3.45 (6H, s), 3.72 (3H, s), 5 85 (1H, m), 5 95 (1H, s)

E and Z 2S,4S,5R 2-butenoic acid, 3-[4-methyl-3-[(4-methylphenyl)sulfonyl]-5-phenyl-2-oxazolidinyl] methyl ester 5a and 3-oxazolidinecarboxylic acid, 2-(3-methoxy-1-methyl-3-oxo-1-propenyl)-4-methyl-5-phenyl methyl ester 5b

General cyclization procedure:

BF_3Et_2O (2 eq) was added to a (0 2 M) solution of **4** (1 eq) and (1R,2S) N-protected nor-ephedrine (1 eq) in dry benzene After stirring for 10 min[16] the reaction mixture was washed with aqeous $NaHCO_3$ and extracted with Et_2O The combined organic extracts were dried over Na_2SO_4, filtered and the solvent evaporated under reduced pressure The crude product was purified by flash chromatography Chromatographic separation of the E/Z isomers could be easily effected only on **5a** (n-Hexane/Ethyl acetate) **5a-Z.** ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 1 00 (3H, d, J=7 1 Hz), 2 15 (3H, s), 2 50 (3H, s), 3 79 (3H, s), 3 97 (1H, m), 4 39 (1H, d, J=6 0 Hz), 5 31 (1H, s), 6 08 (1H, s), 7 08-8 01 (9H, m) **5a-E** ^{1}H-NMR ($CDCl_3$) δ 0 88 (3H, d, J= 7 1 Hz), 2 30 (3H, s), 2 49 (3H, s), 3 78 (3H, s), 4.18 (1H, m), 4 53 (1H, d, J=6 0 Hz), 5 38 (1H, s), 6 12 (1H, s), 7 08-8 01 (9H, m) m p 116-7°C (i-Pr_2O) **5a**· ^{13}C-NMR ($CDCl_3$, 50 MHz) δ 13 65, 17 34, 21 66, 51 3, 58 55, 81 66, 93 29, 120 2, 125 87, 127 88, 128 14, 128 43, 130 08, 134 92, 135 02, 144 55, 152 75, 166 55 (selected values) IR ($CHCl_3$) ν 3020, 2980, 2940, 2864, 1720, 1660, 1595, 1430, 1450, 1350 cm^{-1} **5b E** and **Z** ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 0 88 (3H, d, J=6 9 Hz), 2 27 (3H, s), 3 72 (6H, 2s), 4 37 (1H, m), 5 17 (1H, d, J=6 0 Hz), 5 47 (1H, s), 6 11 (1H, s), 7.21-7 47 (5H, m) ^{13}C-NMR ($CDCl_3$, 50 MHz) δ 13 42, 16 17, 51 18, 52 63, 56 30, 81 50, 91 90, 119 69, 126 05, 127 90, 128 30, 135 51, 135 70 (selected values) IR ($CHCl_3$) ν 3040, 2966, 2950, 2891, 1720, 1445, 1361, 1160 cm^{-1}

Hydrogenation of 5a and 5b:

method a

A (0 03M) solution of **5a** or **5b**[17] (1eq) in MeOH was hydrogenated (1 atm H_2) in the presence of a catalytic amount of 10% Pd/C (0 03 eq) After 3 h stirring at room temperature the mixture was filtered through Celite^R washing with EtOH The solvent was removed in vacuo and the residue was purified by flash chromatography (n-hexane/AcOEt 75/25)

method b

$NaBH_4$(40 eq) was added to a (0 05 M) solution of **5a** or **5b**[17] (1eq) and $CoCl_2$ (2 eq) in MeOH/THF (5 1) at 0 °C with stirring After 2 5 h the resulting mixture was filtered through a Celite^R pad washing with Et_2O The organic layer was dried over Na_2SO_4, filtered and the solvent evaporated The residue was purified by flash chromatography (n-hexane/AcOEt 75/25) (2'R)-**3** EWG= Ts. ^{1}H-NMR ($CDCl_3$, 200 MHz) 0 81 (3H, d, J=7 1 Hz), 1 21 (3H, d, J=6 6 Hz), 2 22-2 96 (3H, m), 2 48 (3H, s), 3 63 (3H, s), 4 02 (1H, m), 4 31 (1H, d, J=5 7 Hz), 4 98 (1H, d, J=3 8 Hz), 7 04-7 92 (9H, m) ^{13}C-NMR ($CDCl_3$, 50 MHz) δ 16 29, 17 37, 21 59, 35 04, 51 60, 58 53, 80 70, 94 04, 125 84, 127 95, 128 28, 129 61, 173 38 (selected values) IR ($CHCl_3$) ν 3030, 1970, 1870, 1731, 1595, 1490, 1450, 1430, 1349 cm^{-1} (2'R)-**3** EWG= CO_2Me ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 0 81 (3H, d, J=7 1 Hz), 1 18 (3H, d, J=7 0 Hz), 2 21-2 72 (2H, m), 2 83 (1H, m), 3 71 (3H, s), 3 78 (3H, s), 4 30 (1H, m), 5 04 (1H, d, J=2 4 Hz), 7 23-7 48 (5H, m) ^{13}C-NMR ($CDCl_3$, 50 MHz) δ 16 2, 16 4, 33 0, 34 9, 51 5, 52 5, 56 5, 80 7, 92 9, 126 0, 127 8, 128 3, 135 9, 155 0, 173 6 (selected values) IR ($CHCl_3$) ν 2970, 1725, 1692, 1445, 1365 cm^{-1}

method c (for **5b**)

A solution of **5b** (56 5 mg, 0 18 mmol) in THF/H_2O 5/1 (3 5 ml) was treated with a 1 0 M THF solution of SmI_2 (8 8 ml, 0 88 mmol) at room temperature and under nitrogen, until a persistent blue color was obtained The mixture was extracted with Et_2O The organic extracts were dried over Na_2SO_4, filtered and the solvent evaporated under reduced pressure The crude product was purified by flash chromatography (n-hexane/AcOEt 75/25) to give (2'S)-**3** EWG= CO_2Me in 33% yield (2'S)-**3** EWG= CO_2Me ^{1}H-NMR ($CDCl_3$, 200 MHz)· δ 0 82 (3H, d, J=7 1 Hz), 1 05 (3H, d, J=6 1 Hz), 2 25-2 70 (2H, m), 2 85 (1H, m), 3 71 (3H, s), 3 76 (3H, s), 4 81 (1H, m), 5 04 (1H, d, J=2 8 Hz), 5 14 (1H, d, J=6 0 Hz), 7 25-7 46 (5H, m)

^{13}C-NMR ($CDCl_3$, 50 MHz) δ 12.74, 16 06, 32 7, 37 7, 51 58, 52.51, 56 34, 80 556, 91 12, 125 9, 127 7, 128 2 (selected values)

Acknowledgements

Support by Consiglio Nazionale delle Ricerche (Progetto Chimica Fine II) and Ministero dell'Universita' e della Ricerca Scientifica are gratefully acknowledged We also thank Prof Carlo Scolastico for helpful discussions and Dr Umberto Piarulli for his enthusiastic technical assistance

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4 The procedure described in Ref 1f was modified, see experimental

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9 The following methods for the double bond reduction in **5a** or **5b** failed 1,4 hydride delivery with L-Selectride[10] or hydridocuprates,[11] hydrostannation with $HSnBu_3$,[12] homogeneous catalytic hydrogenation with [Rh(Diphos-4)NBD]BF_4[13] or [Ir(COD)pyPCy$_3$]PF_6[13]

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14 Experimental procedure for oxazolidine cleavage and methods of e e determination of **1** have been described in ref 2

15 Details on the mechanism of the SmI_2 promoted reduction of activated double bonds are not available, however, analogy with the corresponding carbonyl reduction suggests that carbanionic protonation at C3' is the stereochemically deciding step

16 Care must be taken with the reaction time in order to avoid E/Z isomerization

17 The same reaction was carried out on compound **2b** using D_2 or $NaBD_4$