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ALKYLATION OF CHIRAL PROLINOL PROPIONAMIDE ENOLATES WITH EPOXIDES: COMPLETE REVERSAL OF PREDICTED FACIAL SELECTIVITY

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Summary: The title transformation provided a rapid and efficient synthesis of syn and anti 2-methyl-4-hydroxylcarboxylic ester arrays.

In connection with our efforts directed towards the total synthesis of the highly potent and selective immunosuppressant FK-506[1], and in particular the C.10-C.18 segment[2] 1, we have been interested in the development of methodology for the stereoselective synthesis of 2-methyl-4-hydroxyl-carboxylic ester arrays, eg. 2 and 3 (X=OR'). In principle, 2 and 3 could be prepared by alkylation of the highly nucleophilic propionamide enolates (R)-4 and (S)-4[3] with the primary epoxide 5. The stereochemistry of the product hydroxy-amides (syn(2) or anti(3); (X=1-(2-hydroxymethylpyrrolidine)-yl)) would be controlled by the chirality of the epoxide electrophile and the propionate enolate equivalent[4]. The alkylation of terminal epoxides with achiral propionamide enolates has been demonstrated[5]; however these reactions typically suffer from low diastereoselectivity. The alkylation of chiral prolinol amide enolates with achiral and chiral halide electrophiles has also been investigated; the stereochemistry of such alkylations can be readily predicted.[3] We have investigated the use of chiral prolinol propionamide enolates 4 for these transformations. We wish to record here a surprising reversal of expected facial selectivity in the reaction with terminal epoxides.

Treatment of epoxide 5[6,7] (b.p. 88-90°C, 0.5 torr; $[\alpha]_D^{25}$ = -25.3°, c 1.03, CH_2Cl_2, ≥97% ee[8]) with 5 equivalents of enolate (S)-4, which possesses a very strong facial bias towards alkylation from the pro-2(R) face, (THF, -30°C) followed by hydrolysis of the resulting amides 2 and 3 (X=1-(2-hydroxymethyl-pyrrolidine)-yl) gave the lactones 6 ($[\alpha]_D^{25}$=-14.1°, c 0.41, CH_2Cl_2) and 7 ($[\alpha]_D^{25}$=-30.6°, c 1.04, CH_2Cl_2) (85%).[9] Surprisingly, the undesired cis lactone 7 was obtained as the major species (Table I, entry 1). This result implies attack on the epoxide by enolate (S)-4 from the more hindered pro-2(S) face (syn to $-CH_2OLi$). Similarly, alkylation of the antipodal enolate (R)-4 with 5 under the same conditions followed by hydrolysis gave reversed facial attack from the pro-2(R) face, affording almost exclusively (98:2) the desired trans lactone 6 in 90% yield (entry 2).[10]

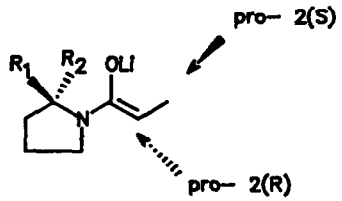
To further probe the effect of the electrophilic species in this reaction, epoxide 5 was converted to the corresponding t-butyldimethylsilyl protected iodohydrin 8.[11] Alkylation of the enolate (S)-4 with 8 (THF, 25°C, 48h) afforded the amides 9 and 10 (X=1-(2-hydroxymethylpyrrolidine)-yl) which were directly subjected to acidic hydrolysis-lactonization. Lactones 6 and 7 were thus obtained (77%) with the desired trans isomer 6 as the major species (entry 3). This corresponds to attack of the electrophilic iodide from the least hindered pro-2(R) face of enolate (S)-4 (anti to $-CH_2OLi$). Similarly, alkylation of the antipodal enolate (R)-4 with 8 resulted in attack from the pro-2(S) face, albeit with attenuated selectivity (entry 4).

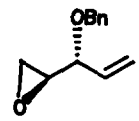
The epoxide 11[12], prepared from lactone 6 via the bromocarbonate 12[2,9], mp 89.5-90.5°C, was also investigated. It should be noted that although 11 is also an (S)-chiral epoxide, it has the opposite relationship with the benzyloxy-substituent (syn) compared to epoxide 5 (anti). Treatment of 11 with the enolate (S)-4 followed by hydrolysis gave highly selective formation of the cis-lactone 13, the product arising from attack of enolate (S)-4 from the pro-2(S) face (syn to $-CH_2OLi$, entry 5). Enolate (R)-4 reacted with epoxide 11 to provide mostly the desired trans-lactone 14, although the selectivity was poor (entry 6).

Table I Diastereoselective alkylations of enolates (S)-4 and (R)-4 with Compounds 5, 8 and 11

Entry	Electrophile	Enolate	Ratio(2S/2R)[e]	Yield[f]	Facial Attack
1	5	(S)-4[a,c]	87/13 (7:6)	85%	Syn to ($-CH_2OLi$)
2	5	(R)-4[a,c]	2/98 (7:6)	90%	"
3	8	(S)-4[a,d]	7/93 (7:6)	77%	Anti
4	8	(R)-4[a,d]	75/25 (7:6)	79%	"
5	11	(S)-4[b,d]	96/4 (13:14)	76%	Syn
6	11	(R)-4[b,d]	30/70(13:14)	83%	"

a) 5 eq. of enolate used, b) 10 eq. of enolate used, c) reaction at -30°C, d) reaction at +25°C, e) ratio based on capillary gc analysis of the crude reaction mixtures, f) isolated yield of butyrolactones after silica gel column chromatography.





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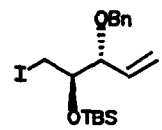
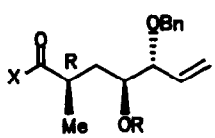
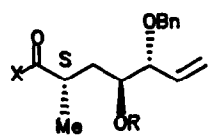


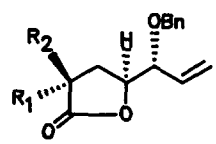
8

(S)-4 R_1 = $-CH_2OLi$, R_2 = H

(R)-4 R_1 = H, R_2 = $-CH_2OLi$







2 R = H

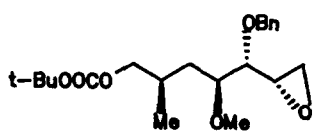
9 R = TBS

3 R = H

10 R = TBS

6 R_1 = Me, R_2 = H

7 R_1 = H, R_2 = Me



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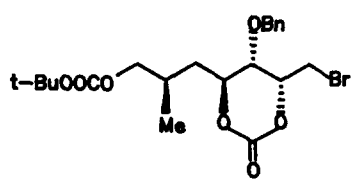

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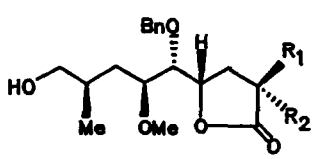
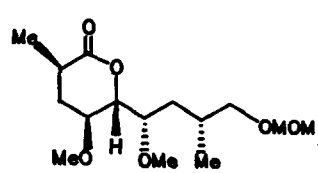


13 R_1 = H, R_2 = Me

14 R_1 = Me, R_2 = H



1

The exact reason for the reversal of prolinol enolate facial selectivity in the alkylation with epoxides remains unclear. One possibility for the reversed selectivity is that intermolecular chelation of the basic epoxide oxygen to the lithio-alkoxymethyl group directs alkylation from the apparently more hindered face of the enolate.[13] The novel methodology outlined herein provides a rapid and efficient entry into syn and anti 2-methyl-4-hydroxyl-carboxylic ester arrays.

References and Notes

1) Tanaka, H.; Kuroda, A.; Marusawa, H.; Hatanaka, H.; Kino, T.; Goto, T.; Hashimoto, M. J. Am. Chem. Soc. 1987, 109, 5031.
2) Askin, D.; Volante, R.P.; Reamer, R.A.; Ryan, K.M.; Shinkai, I. Tetrahedron Lett. 1988, 29, 277.
3) (a) Evans, D.A.; Takacs, J.M. Tetrahedron Lett. 1980, 21, 4233. (b) Sonnet, P.E.; Heath, R.R. J. Org. Chem. 1980, 45,3137. (c) For a review of chiral enolate equivalents, see: Evans, D.A. Aldrichimica Acta 1982, 15, 23.
4) a) Heathcock, C.H.; White, C.T.; Morrison, J.; VanDerveer, D. J. Org. Chem. 1981, 46, 1296. (b) Masamune, S.; Choy, W.; Petersen, J.S.; Sita, L.R. Angew. Chem., Int. Ed. Engl. 1985, 24, 1.
5) Sauriol-Lord, F.; Grindley, T.B. J. Org. Chem. 1981, 46, 2831, and references therein.
6) (a) All new compounds reported gave satisfactory 300 MHz ^{1}H NMR, ^{13}C NMR, IR and mass spectral data. (b) Compounds 5-8, 11-12 gave satisfactory elemental analysis; compounds 13 and 14 gave satisfactory high resolution mass spectral analysis.
7) For leading references to the parent epoxy-alcohol of 5, see: (a) Hatakeyama, S.; Sakurai, K.; Takano, S. J. Chem. Soc., Chem. Commun. 1985. 1759. (b) Häfele, B.; Schröter, D.; Jäger, V. Agnew. Chem., Int. Ed. Engl. 1986, 25, 87. (c) Babine, R.E. Tetrahedron Lett. 1986, 27, 5791. (d) Schreiber, S.L.; Schreiber, T.S.; Smith, D.B. J. Am. Chem. Soc. 1987, 109, 1525.
8) Determined by ^{19}F NMR analysis on the derived Mosher esters of the parent epoxy-alcohol: Dale, J.A.; Dull, D.L.; Mosher, H.S. J. Org. Chem. 1969, 34, 2543.
9) The stereochemistry of 6, 7, 12, 13 and 14 was unambiguously determined by NOE difference spectroscopy.
10) Treatment of epoxide 5 with 5 equivalents of lithio-pyrrolidine propionamide (THF, 0°C, 24h) gave the corresponding amides which were directly subjected to acidic hydrolysis (1N HCl, dioxane, 100°C, 3h) without isolation. The lactones 6 and 7 were isolated (63/37 respectively) in 86% overall yield. Conducting the alkylation at -30°C did not improve the ratio of 6:7.
11) (a) Treatment of 5 with trimethylsilyl iodide (toluene, -78°C to -50°C, 2h) selectively afforded the 2-trimethylsilyloxy-1-iodide which after desilylation (methanol, 25°C, 1 h), and reprotection (t-butyldimethylsilyl triflate/2,6-lutidine, CH_2Cl_2, 25°C) gave 8 (99%). The regiochemistry of iodide attack was confirmed by ^{13}C NMR/APT spectroscopy on the intermediate iodohydrin: 10.1 ppm, CH_2 group. (b) Denis, J.N.; Krief, A. Tetrahedron Lett. 1981, 22, 1429.
12) Attempted protection of the iodohydrin obtained from epoxide 11 could not be achieved due to the highly hindered nature of the hydroxyl group and the propensity to undergo cyclization with loss of methyl iodide to a tetrahydrofuran.
13) Preliminary results obtained upon reaction of enolates (R)-4 and (S)-4 with (S)-propylene oxide also indicate a reversal of facial selectivity. Experiments with other simple chiral and achiral epoxides will be reported in a full paper.

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