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Diastereoselective *Syn*-Epoxidation of 2-Alkyl-4-Enamides to Epoxyamides: Synthesis of the Merck HIV-1 Protease Inhibitor Epoxide Intermediate.

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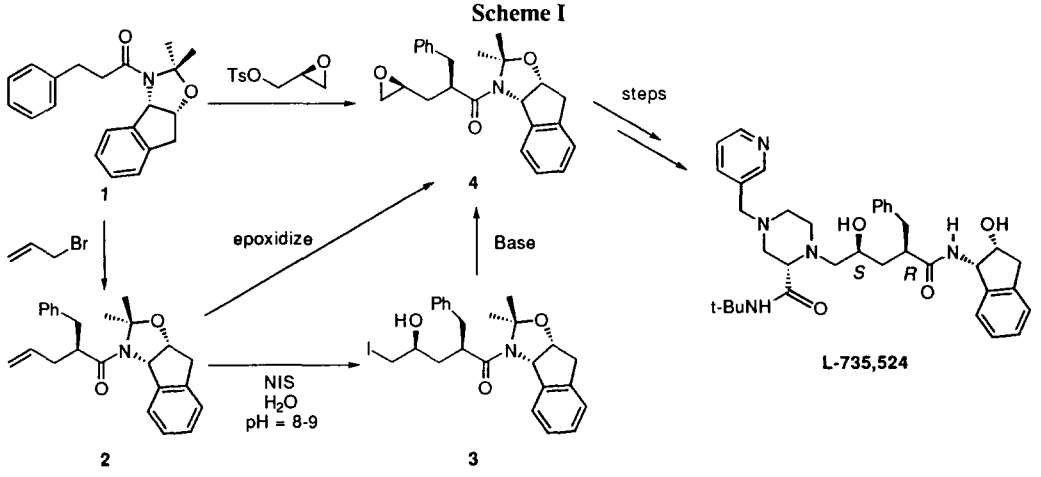
Abstract: *Reaction of 2-alkyl-4-enamides* ***2, 9-15*** *with NIS and aqueous sodium bicarbonate results in the diastereoselective formation of the corresponding iodohydrins* ***3, 16-22*** *with essentially no iodolactone by-product. This methodology has been successfully employed for the synthesis of the epoxide intermediate* ***4*** *of the orally active Merck HIV-1 protease inhibitor L-735,524.*

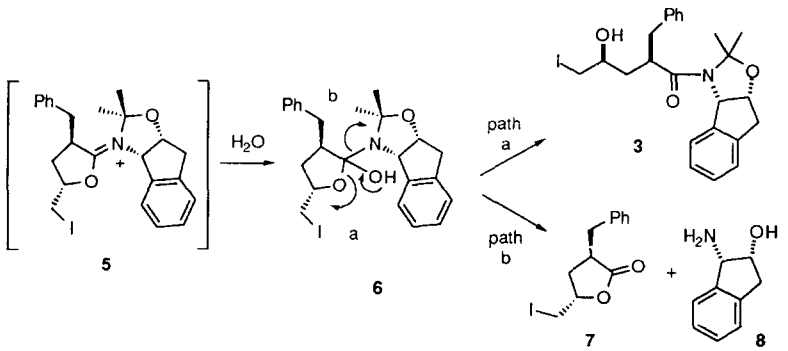
The orally active HIV protease inhibitor L-735,524[1] is one of a group of new agents currently in advanced clinical trials for the treatment of AIDS. L-735,524 is derived from the key intermediate epoxide **4** (Scheme I), which has been prepared in 72% yield by the condensation of the lithium *(Z)*-enolate of **1** and *(S)*-glycidyl tosylate[2]. An alternate route to **4** involves diastereoselective allylation of **1** to provide **2** followed by *syn*-epoxidation. Herein we wish to report an improved synthesis of **4** from **1** via a three-step process involving: a) diastereoselective allylation of the lithium (Z)-enolate of **1**, b) diastereoselective conversion of **2** to iodohydrin **3** via NIS mediated cyclic iodoimidate formation and hydrolysis and c) base mediated conversion of **3** to epoxide **4**. This procedure eliminates (S)-glycidyl tosylate from the process and produces epoxide **4** in 97:3 diastereoselectivity from **2**.

Scheme I



Allylation of **1** with lithium hexamethyldisilazide (LHMDS) and allyl bromide at -15 °C in THF affords a 96:4 ratio of **2** (94%) and the benzyl diastereomer **15**. Previous attempts to convert **2** to **3** via diastereoselective cyclic iodoimidate formation and subsequent hydrolysis following standard protocols (iodine in aqueous THF[3]) led to amide cleavage and iodolactone formation[4,5]. However, after screening a series of halogenating agents and reaction conditions[6], it was found that NIS in the presence of aqueous bicarbonate effected remarkably efficient and selective conversion of **2** to iodohydrin **3**.[6b] The reaction proceeds well in dichloromethane, ethyl acetate, or isopropyl acetate (IPAc)[6c] with aqueous sodium bicarbonate or moist basic alumina as bases. Under these conditions, the iodohydrin **3** is presumably formed via ring opening of the tetrahedral intermediate **6** derived from **5** (Scheme II).

Scheme II



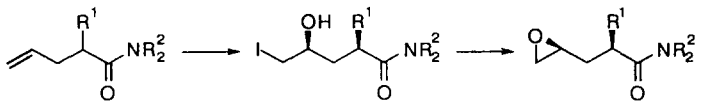
Since NIS is currently commercially available only in limited quantities, the reaction of readily available NCS and NaI was investigated as a practical source of NIS.[7] Interestingly, N-chlorosuccinimide (NCS) did not react with **2**, allowing for potential *in-situ* generation of the reactive NIS reagent. *Thus, treatment of a mixture of olefin* **2** *and NCS (1.7 equiv) in IPAc/aqueous sodium bicarbonate with an aqueous solution of NaI (1.7 equiv) gave after 1h at 20 °C the desired iodohydrin* **3** *in 92% yield and 97:3 diastereoselectivity without any detectable formation of the undesired iodolactone 7.* The resulting IPAc solution of **3,** after quenching with aqueous Na_2SO_3, was treated with a 25% solution of sodium methoxide (1.2 equiv) to afford the epoxide **4** in 99-100% yield.[8] The overall yield from **1** to **4** was 86% on a multikilogram scale.

To further examine the generality of this process, a series of *N,N*-dialkyl-2-substituted-4-enamides **9-15** (Table I) were prepared.[9] In general, the corresponding iodohydrins **16-22** were formed in high yield with good to excellent diastereoselectivity.[10] The iodohydrins were readily converted to the corresponding syn-epoxides by treatment with base (KOt-Bu or NaOMe in THF). Interestingly, the unsubstituted case **14** gave a lower yield of iodohydrin **21** due to oxidation at the 2-position.[11]

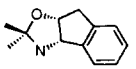
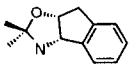
In 2-oxygenated cases, the benzyloxy substituted substrate **12** gave lower diastereoselectivity (2:1) in the iodohydrin formation than the bulky t-butyldiphenylsilyl (TPS) ether substrate **13**[12] (9:1).[13] Comparison of the results obtained from the 2-benzyl diastereomers **2** and **15** shows that the 2-alkyl substituent completely overrides any stereochemical influence from the indanol moiety which might have lead to double diastereoselection.

Table I

Syn-Epoxidation of 2-Alkyl-4-Enamides with NIS



A B

entry	A	B	R^1	NR_2^2	yield[a]	ratio (syn:anti)[b]
1	**9**	**16**	Bn	NEt_2	94[f]	97:3[e,f,h,i]
2	**10**	**17**	Cy-$C_6H_{11}CH_2$	NMe_2	95[f]	15:1[f,i]
3	**11**	**18**	Me	NEt_2	96[c]	20:1[c,i]
4	**12**	**19**	OBn	NEt_2	90[d]	2:1[d,i]
5	**13**	**20**	OSit-$BuPh_2$	NEt_2	90[d]	9:1[d,i]
6	**14**	**21**	H	NEt_2	55[c]	-
7	**2**	**3**	Bn		90[g,j]	97:3[g,h]
8	**15**	**22**	Bn		90[g]	97:3[g,h]

a) All reactions were run with solid NIS (1.3 equiv) and 2.0 equiv $NaHCO_3$ 0.3 M in biphasic organic/aqueous mixtures. Yields represent chromatographically and spectroscopically homogeneous (^{13}C and ^1H NMR) material isolated by silica gel flash chromatography unless otherwise stated. b) Ratio determined on crude reaction mixture (organic phase of iodohydrin formation reaction or organic phase after addition of water to the epoxide formation reaction mixture). c) Iodohydrin formation performed in EtOAc (0.3 M, 20 °C) d) Iodohydrin formation in EtOAc (0.3 M, 0 °C) e) Iodohydrin formation in dichloromethane (0.3 M, 20 °C) f) After epoxide formation performed in THF (0.3 M, 20 °C). g) Iodohydrin formation performed in isopropyl acetate (0.3 M, 20 °C). h) Ratio determined by HPLC analysis; (150 x 4.6 mm YMC-Pack C-8 column at 40 °C, 0.1M $NH_4H_2PO_4$/methanol, gradient 60/40-20/80 (v/v) over 40 min, 220 nm detection. i) Ratio determined by integration of resolved peaks in ^{13}C and ^1H NMR spectra. j) Yield determined by quantitative HPLC.

We are currently examining further generalization of this chemistry, as well as subtle factors controlling selectivity in the hydrolysis of cyclic iodoimidates.

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6. (a) A variety of halohydrin formation protocols were tried with the following reagents: iodine, bromine, iodine chloride, iodine bromide, sodium hypochlorite, trichloromelamine, dichlorodimethylhydantoin, tetrabromocyclohexadienone, iodonium di-*sym*-collidine perchlorate, *N*-chlorosuccinimide (NCS), *N*-bromosuccinimide (NBS), and *N*-iodosuccinimide (NIS) in aqueous organic solvents (THF, acetonitrile, and dichloromethane) in the presence of bases such as sodium bicarbonate, sodium carbonate, pyridine, and diisopropylethylamine. These reagents/conditions led either to iodolactone formation, no reaction, or the formation of complex mixtures. (b) Spectral data for **3** (major rotamer): ^{13}C NMR: (62.5 MHz, $CDCl_3$) 172.2, 140.6, 140.4, 139.3, 129.5, 128.8, 128.2, 127.2, 126.8, 125.7, 124.0, 96.9, 79.1, 68.7, 65.8, 43.7, 40.6, 39.0, 36.6, 26.5, 24.3, 16.3. (c) When the reaction was carried out in diethoxymethane ca. 20% of the 2-benzyl-2-iodo-4-iodomethylactone was isolated.

7. Vankar, Y.D.; Kumaravel, G. *Tetrahedron Lett.* **1984**, *25*, 233-236.

8. The epoxide formation from iodohydrin is reversible upon extended aging in the presence of water.

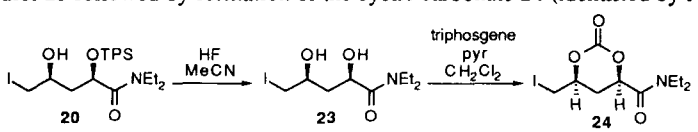
9. (a) The 2-substituted-4-enamides **9-14** were prepared by alkylation of the appropriate tertiary amides with allylbromide in the presence of LHMDS in THF at -20 °C. The reaction mixture was then warmed to 0 °C and water washed followed by either a 1M aqueous HCl wash or (in the case of an acid labile product) a 0.2M H_2SO_4 wash; after a further water wash and an aqueous $NaHCO_3$ wash the organic phase was dried ($MgSO_4$), evaporated and chromatographed on silica gel (94-99%). (b) The benzyl diastereomer **15** was prepared by acylation of (1S, 2R)-1-amino-2-indanol with 4-pentenoyl chloride (IPAc, aq. NaOH), followed by acetonide formation (2-methoxypropene, cat. MsOH, IPAc) and diastereoselective benzylation (BnBr, LHMDS, THF, -15°C) and recrystallization.

10. Stereochemistry of iodohydrin **16** confirmed by conversion to the corresponding anti-iodolactone (5 equiv $MeSO_3H$, THF) whose stereochemistry was confirmed by NMR and N.O.E. studies.

11. Treatment of pentenamide **14** with NIS/aq $NaHCO_3$ in CH_2Cl_2 gave ca. 10% of the expected iodohydrin, 30% of α-iodo-iodohydrin, and 10% of α-keto-iodohydrin.

12. The silyl ether **12** was prepared by conversion of glycolic acid to its acetonide (3 equiv of 2-methoxypropene, 20 °C) which was treated with diethylamine (2 equiv, 55 °C) to afford the corresponding hydroxyamide (62% from glycolic acid). Khalaj, A.; Nahid, E.; *Synthesis* **1985**, 1153-1155. Protection of the hydroxyamide as its tetrahydropyranyl ether (1.1 equiv dihydropyran, cat. p-toluenesulfonic acid, 45 °C), alkylation with allyl bromide (1.2 equiv LHMDS, THF, -20 °C), deprotection (HCl, methanol, 20 °C), and silylation (1.1 equiv TPSCl, 1.5 equiv imidazole, DMF, 20 °C) gave **12** (91% from 2-hydroxy-diethylacetamide).

13. The *syn* stereochemistry of the major diastereomer of iodohydrin **20** was confirmed by conversion to diol **23** followed by formation of the cyclic carbonate **24** (identified by NMR and N.O.E. studies).



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