Regioselective Reduction of 3-Methoxymaleimides: an Efficient Method for the Synthesis of Methyl 5-Hydroxytetramates

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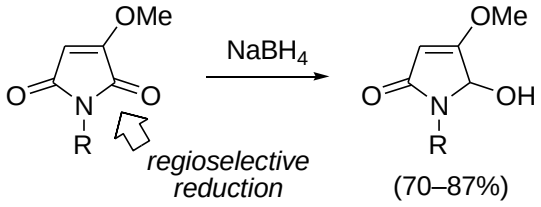
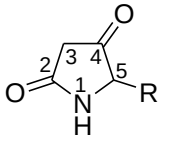
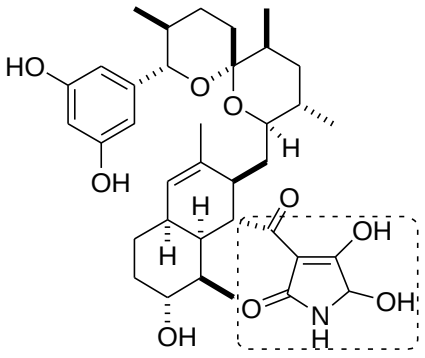


Abstract. 3-Methoxymaleimide and various *N*-alkyl-3-methoxymaleimides, synthesized by base-promoted *N*-alkylation of 3-methoxymaleimide, were reduced using sodium borohydride with complete regioselectivity. The resultant methyl 5-hydroxytetramates are useful intermediates in the synthesis of a variety of tetramate derivatives.

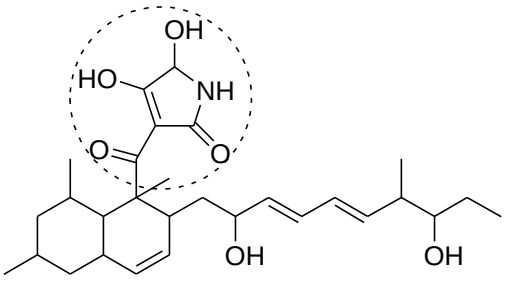
Tetramic acids (pyrrolidine-2,4-diones) **1** are a common structural feature in a number of biologically-active natural products, including compounds with antibacterial, antifungal and cytotoxic properties.[1] 5-Hydroxytetramic acids (5-hydroxypyrrolidine-2,4-diones) **2**, which exhibit an *N*-acylhemiaminal functionality, are less common, though still represented in the HIV-integrase inhibitory and immunomodulatory/antibacterial natural products integramycin (**3**)[2] and delaminomycin A (**4**),[3] respectively. A direct and convenient approach to the synthesis of 5-hydroxytetramic acids would rely on the regioselective reduction of a suitable maleimide derivative. Given the ready availability of 3-methoxymaleimide (**5a**),[4] and the known facility with which *O*-alkyl tetramates can be hydrolyzed to tetramic acids,[5] the regioselective reduction of 3-methoxymaleimides and subsequent hydrolysis appeared to be a potentially convenient route to 5-hydroxytetramic acids.



1: R = H, alkyl
2: R = OH



3: integramycin

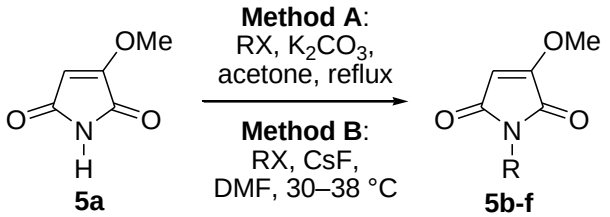


4: delaminomycin A

3-Methoxymaleimide (**5a**) is readily available from maleimide by a convenient two step procedure.[4] A variety of *N*-alkyl-3-methoxymaleimides **5b-f** were prepared by base-promoted

alkylation of **5a** (Table 1). The potassium carbonate promoted *N*-benzylation[6] and *N*-methylation[7,8] of maleimides with benzyl bromide and iodomethane, respectively, in acetone solvent, have previously been reported. Reaction of **5a** with a variety of alkylating agents under these conditions (Method A), provided the desired *N*-alkyl-3-methoxymaleimides **5b-f** in good yields (87–92%) when MeI, EtI or PMBCl were employed (entries 1, 2 and 5). The use of MeCN as solvent markedly improved the yield of **5e** (99% vs. 55% with acetone), however this procedure with either solvent did not prove satisfactory for the allylation of **5a** to give **5d** (10% with acetone vs. 2% with MeCN). An alternative procedure, employing cesium fluoride in DMF (Method B), inspired by the facile CsF-promoted *N*-alkylation of phthalimide with alkyl chlorides reported by Clark and Miller,[9] proved to be facile for most alkylations, including the reaction of **5a** with allyl chloride (84%). 3-Methoxy-*N*-phenylmaleimide (**5g**) was prepared in three steps from *N*-phenylmaleimide by the method of Argade,[10] as another substrate for the regioselective reduction.

Table 1. Alkylation of methoxymaleimide (**5a**)[a]



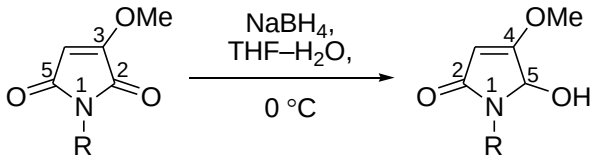
entry	R–X	product	Method A yield (%)[b]	Method B yield (%)[b]
1	MeI	**5b**	87	90
2	EtI	**5c**	92	61
3	Allyl chloride	**5d**	10	84

4	BnCl	**5e**	99[c]	94
5	PMBCl	**5f**	91	68

[a] **Method A**: **5a**, RX (2–2.9 equiv.), K_2CO_3 (1.2 equiv.), acetone, reflux, 17–90 h; **Method B**: **5a**, RX (3 equiv.), CsF (3 equiv.), DMF, 30–38 °C, 24 h. [b] Isolated yields. [c] MeCN as solvent, 50 °C (55% yield with acetone).

Citraconimide (3-methylmaleimide), and *N*-alkyl derivatives, have previously been shown to undergo regioselective reduction with sodium borohydride to give predominantly the products of attack at the more hindered C2 position (88 : 12 → >99 : <1), whereas a reversal in regioselectivity was observed with $NaBH_4$ in the presence of cerium(III) chloride heptahydrate ($CeCl_3 \cdot 7H_2O$) or by using diisobutylaluminum hydride (DIBAL-H).[11] We reasoned that delocalisation of a lone pair on the methoxy oxygen of **5a-g** would significantly decrease the reactivity of the C5 carbonyl group towards nucleophilic attack by hydride reducing reagents, and that for this reason, the reduction of these systems should be particularly regioselective.[12] A survey of common reducing agents showed DIBAL-H, in THF or CH_2Cl_2, to be surprisingly non-selective in its reaction with **5e**, providing *ca*. 1:1 mixtures of regioisomeric reduction products. Reduction of **5e** with $LiAlH_4$ gave an 88:12 mixture of products resulting from attack at C2 and C5 respectively, and appreciable quantities of over-reduced compounds. The use of $NaBH_4$–$CeCl_3$ improved the regioselectivity to 97:3 in favour of the C2 reduced compound, however, the use of $NaBH_4$ by itself, in THF–H_2O at 0 °C proved particularly effective and convenient, providing **6e** as the sole isolated regioisomer in 83% yield (Table 2, entry 5). In all cases studied (Table 2), these conditions provided good yields (70–87%) of the methyl 5-hydroxytetramates **6a-g**, with no evidence for the formation of the regioisomeric products, resulting from borohydride attack at C5 of **5a-g**.

Table 2. Regioselective reduction of **5a-g**



5a-g **6a-g**

entry	substrate	R	t/min	product [a]
1	**5a**	H	30	**6a** (87%)
2	**5b**	Me	45	**6b** (87%)
3	**5c**	Et	90	**6c** (84%)
4	**5d**	allyl	30	**6d** (85%)
5	**5e**	Bn	100	**6e** (83%)
6	**5f**	PMB	180	**6f** (76%)
7	**5g**	Ph	60	**6g** (70%)

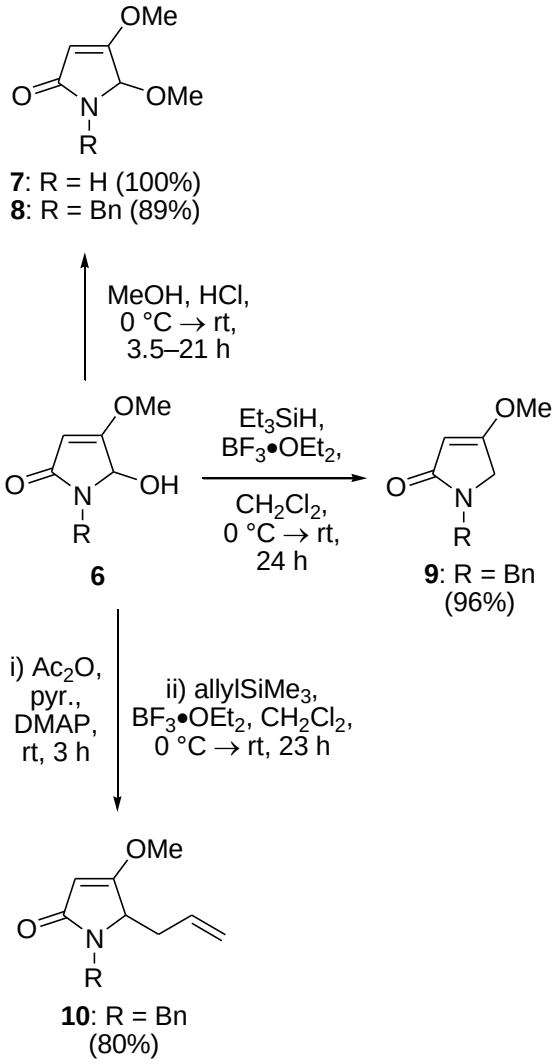
[a] Isolated yields.

The physical and spectroscopic data, *eg*. ^{1}H and ^{13}C NMR, for **6a** and **6b** match that reported previously,[12,13] while the structure of **6e** was confirmed by single crystal X-ray diffraction, the ORTEP depiction is provided in the Supporting Information. The structures of **6c-d,f-g**, and therefore the regioselectivity of the reduction, were assigned by analogy with the aforementioned, closely related examples.[14]

Attempts to hydrolyze methyl 5-hydroxytetramates **6a** and **6e** (aq. HCl) have thus far been thwarted by difficulties with purification and/or instability of the resultant 5-hydroxytetramic acids. It is possible that 3-acyl derivatives, such as the natural products integramycin (**3**) and delaminomycin (**4**), are inherently more stable, and as such, future work will be directed towards these types of systems. Nevertheless, methyl 5-hydroxytetramates **6a-g** afforded by the regioselective reduction reported herein, are versatile building blocks for the synthesis of a range of tetramate derivatives (Scheme 1). Treatment of **6a** and **6e** with methanolic HCl afforded

methyl 5-methoxytetramates **7** and **8**, in 100% and 89% yields, respectively. Reduction of **6e** with Et_3SiH and $BF_3{\cdot}OEt_2$ to afford **9** (96% yield), demonstrates that access to methyl *N*-alkyltetramates can be achieved. Acetylation of **6e** (Ac_2O, pyridine, DMAP) followed by treatment of the resultant acetate with allyltrimethylsilane and $BF_3{\cdot}OEt_2$ provided 5-allyltetramate **10** in good yield (80% over two steps).

Scheme 1. Synthesis of Methyl Tetramate Derivatives



Experimental Section

Method A representative procedure: To a solution of 3-methoxymaleimide (**5a**) (40.0 mg, 0.315 mmol) in MeCN (0.52 mL) was added K_2CO_3 (52.2 mg, 0.378 mmol, 1.2 equiv.) and then BnCl (72 μL, 0.63 mmol, 2.0 equiv.) dropwise. The mixture was heated to 50 °C until t.l.c analysis indicated complete conversion of the starting material (90 h). After cooling to rt the reaction mixture was concentrated *in vacuo*, then partitioned between half-saturated aq. NH_4Cl and EtOAc. The layers were separated and the aqueous phase was extracted with EtOAc (2 ×). The combined organic layers were dried ($MgSO_4$), filtered, then the filtrate was concentrated *in vacuo*. Purification of the residue by flash chromatography (hexane/EtOAc 60:40) gave 1-benzyl-3-methoxy-1*H*-pyrrole-2,5-dione (**5e**) as a colourless solid (67.6 mg, 99%): mp 68-69 °C; IR (thin film) 3117, 3032, 1709, 1639 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.27 (m, 5H), 5.39 (s, 1H), 4.62 (s, 2H), 3.85 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 169.6 (C), 165.0 (C), 160.8 (C), 136.1 (C), 128.4 (CH), 128.0 (CH), 127.5 (CH), 96.2 (CH), 58.8 (CH_3), 40.9 (CH_2); MS (ESI) *m/z* 240 $[M + Na]^+$, 218 $[M + H]^+$; HRMS (EI) calcd for $C_{12}H_{11}NO_3$ (M^+) 217.0739, found 217.0737.

Method B representative procedure: To a mixture of 3-methoxymaleimide (**5a**) (63.5 mg, 0.500 mmol) and anhydrous CsF (228 mg, 1.50 mmol, 3.0 equiv.) was added DMF (1.67 mL), followed by allyl chloride (122 μL, 1.50 mmol, 3.0 equiv.). The mixture was heated at 30-38 °C for 24 h. The suspension was diluted with half-saturated aq. $NaHCO_3$ solution and EtOAc, then the layers were separated. The aqueous phase was extracted with EtOAc (5 ×) and the combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification of the residue by flash chromatography (hexane/EtOAc 60:40) provided 1-allyl-3-methoxy-1*H*-pyrrole-2,5-dione (**5d**) as a colourless solid (70.0 mg, 84%): mp 61-63 °C; IR (thin film) 3111, 1705, 1626 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.80 (ddt, J = 17.2, 15.7, 5.5 Hz, 1H), 5.43 (s, 1H),

5.21 (dq, *J* = 7.8, 1.5 Hz, 1H), 5.14 (m, 1H), 4.11 (dt, *J* = 5.6, 1.5 Hz, 2H), 3.94 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 169.6 (C), 165.1 (C), 160.9 (C), 131.5 (CH), 117.5 (CH_2), 96.2 (CH), 58.9 (CH_3), 39.6 (CH_2); MS (ESI) *m/z* 190 $[M + Na]^+$, 168 $[M + H]^+$; HRMS (ESI) calcd for $C_8H_9NO_3Na$ $[M + Na]^+$ 190.0475, found 190.0477.

Representative procedure for the regioselective reduction using $NaBH_4$: To a cooled (0 °C) solution of **5e** (65.5 mg, 0.302 mmol) in 2:1 THF (0.3 mL) and H_2O (0.15 mL), was added $NaBH_4$ (12 mg, 0.31 mmol, 1.0 equiv.). The resulting solution was stirred at 0 °C for 100 min, then quenched by the dropwise addition of acetone (1 mL). Silica gel (0.7 g) was added and the volatile components were removed *in vacuo*. Purification by flash chromatography (MeOH/CH_2Cl_2 5:95) afforded 1-benzyl-5-hydroxy-4-methoxy-1*H*-pyrrol-2(5*H*)-one (**6e**) as a colourless solid (54.9 mg, 83%): mp 134-138 °C; IR (thin film) 3130, 3032, 1655, 1643 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (m, 5H), 5.06 (br d, *J* = ~9 Hz, 1H), 5.00 (s, 1H), 4.94 (d, *J* = 15.1 Hz, 1H), 4.17 (d, *J* = 15.1 Hz, 1H), 3.80 (s, 3H), 3.68 (br d, *J* = ~9 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 173.9 (C), 170.4 (C), 137.2 (C), 128.7 (CH), 128.2 (CH), 127.5 (CH), 93.2 (CH), 80.0 (CH), 58.4 (CH_3), 42.3 (CH_2); MS (ESI) *m/z* 242 $[M + Na]^+$, 220 $[M + H]^+$, 202 $[M - OH]^+$; HRMS (ESI) calcd for $C_{12}H_{13}NO_3Na$ $[M + Na]^+$ 242.0788, found 242.0784.

1-Benzyl-4,5-dimethoxy-1*H*-pyrrol-2(5*H*)-one (8). To a cooled (0 °C) solution of **6e** (100 mg, 0.456 mmol) in MeOH (4.6 mL) was added TMSCl (174 μL, 1.37 mmol, 3.0 equiv.). The reaction was warmed to rt and allowed to stir for 21 h, then the mixture was concentrated *in vacuo*. The residue was dissolved in EtOAc and the organic phase was washed with half-saturated aq. $NaHCO_3$ solution, then brine. The organic phase was dried (Na_2SO_4), filtered and concentrated. Purification of the residue by flash chromatography (EtOAc/acetone 95:5) afforded **8** as a colourless oil (94.8 mg, 89%): IR (thin film) 3107, 3028, 1703, 1634 cm^{-1}; ^{1}H NMR (300

MHz, $CDCl_3$) δ 7.34-7.24 (m, 5H), 5.14 (s, 1H), 5.04 (s, 1H), 4.96 (d, *J* = 14.9 Hz, 1H), 4.02 (d, *J* = 14.9 Hz, 1H), 3.80 (s, 3H), 3.11 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 171.4 (C), 170.0 (C), 137.1 (C), 128.5 (CH), 128.3 (CH), 127.4 (CH), 95.2 (CH), 84.9 (CH), 58.2 (CH_3), 50.4 (CH_3), 42.5 (CH_2); MS (ESI) *m/z* 234 $[M + H]^+$; HRMS (ESI) calcd for $C_{13}H_{16}NO_3$ $[M + H]^+$ 234.1125, found 234.1131.

1-Benzyl-4-methoxy-1*H*-pyrrol-2(5*H*)-one (9). To a cooled (0 °C) suspension of **6e** (40.5 mg, 0.185 mmol, 1.0 equiv.) in CH_2Cl_2 (1.3 mL) was added triethylsilane (59 μL, 0.37 mmol, 2.0 equiv.), followed by $BF_3{\cdot}OEt_2$ (47.0 μL, 0.370 mmol, 2.0 equiv.). The mixture was slowly warmed to rt and stirred for 24 h. The solution was quenched with saturated aq. K_2CO_3 solution, then the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 ×) and the combined organic portions were dried (Na_2SO_4), filtered and concentrated. Purification by flash chromatography (EtOAc/acetone 95:5) afforded **9** as a colourless solid (36.1 mg, 96%): mp 44-45 °C; IR (thin film) 3028, 1674, 1624 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34-7.22 (m, 5H), 5.10 (s, 1H), 4.57 (s, 2H), 3.76 (s, 3H), 3.72 (s, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 173.3 (C), 172.0 (C), 137.4 (C), 128.6 (CH), 127.8 (CH), 127.4 (CH), 94.1 (CH), 58.0 (CH_3), 49.8 (CH_2), 45.3 (CH_2); MS (ESI) *m/z* 226 $[M + Na]^+$, 204 $[M + H]^+$; HRMS (ESI) calcd for $C_{12}H_{13}NO_2Na$ $[M + Na]^+$ 226.0839, found 226.0836.

5-Allyl-1-benzyl-4-methoxy-1*H*-pyrrol-2(5*H*)-one (10). To a solution of **6e** (76.3 mg, 0.348 mmol, 1.0 equiv.) in pyridine (7.0 mL) at rt was added Ac_2O (329 μL, 3.48 mmol, 10 equiv.) followed by DMAP (4.3 mg, 0.0348 mmol, 0.1 equiv.). After stirring for 3 h, the reaction was quenched with water and extracted with Et_2O (5 ×). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. Purification by flash chromatography (hexane/EtOAc 60:40) afforded 5-acetoxy-1-benzyl-4-methoxy-1*H*-pyrrol-2(5*H*)-one as a colourless solid (77.5

mg, 85%): mp 102-104 °C; IR (thin film) 3115, 1749, 1711, 1641 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.30-7.23 (m, 5H), 6.42 (s, 1H), 5.13 (s, 1H), 4.59 (d, *J* = 15.3 Hz, 1H), 4.41 (d, *J* = 15.3 Hz, 1H), 3.80 (s, 3H), 1.88 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 171.2 (C), 170.5 (C), 170.2 (C), 137.2 (C), 128.4 (CH), 128.0 (CH), 127.3 (CH), 94.5 (CH), 79.2 (CH), 58.5 (CH_3), 43.8 (CH_2), 20.4 (CH_3); MS (ESI) *m/z* 284 $[M + Na]^+$; HRMS (ESI) calcd for $C_{14}H_{15}NO_4Na$ $[M + Na]^+$ 284.0894, found 284.0897. To a cooled (0 °C) solution of 5-acetoxy-1-benzyl-4-methoxy-1*H*-pyrrol-2(5*H*)-one (20.5 mg, 0.0785 mmol, 1.0 equiv.), from the above procedure, in CH_2Cl_2 (0.8 mL), was added $BF_3{\cdot}OEt_2$ (39.8 μL, 0.314 mmol, 4.0 equiv.). After stirring at 0 °C for 10 min, allyltrimethylsilane (37.4 μL, 0.236 mmol, 3.0 equiv.) was added dropwise via syringe. The reaction was stirred at 0 °C for 7 h, then warmed to rt and stirred for another 16 h. After pouring the mixture into water (1 mL), the layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3 ×). The combined organic portions were washed with brine, dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash chromatography (hexane/acetone 60:40) afforded **10** as a colourless oil (17.9 mg, 94%): IR (thin film) 3076, 3028, 1680, 1626 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.34-7.21 (m, 5H), 5.51 (ddt, *J* = 17.1, 10.2, 7.1 Hz, 1H), 5.17 (d, *J* = 15.4 Hz, 1H), 5.10 (s, 1H), 5.07 (m, 1H), 5.06 (m, 1H), 3.98 (d, *J* = 15.4 Hz, 1H), 3.87 (t, *J* = 4.3 Hz, 1H), 3.76 (s, 3H), 2.57-2.38 (m, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 175.3 (C), 171.7 (C), 137.6 (C), 131.0 (CH), 128.6 (CH), 127.9 (CH), 127.4 (CH), 118.8 (CH_2), 94.2 (CH), 58.5 (CH_3), 58.0 (CH), 43.2 (CH_2), 32.6 (CH_2); MS (ESI) *m/z* 266 $[M + Na]^+$, 244 $[M + H]^+$; HRMS (ESI) calcd for $C_{15}H_{17}NO_2Na$ $[M + Na]^+$ 266.1152, found 266.1152.

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Supporting Information Available: Experimental procedures and characterization data for new compounds not included in the Experimental Section; ORTEP depiction and X-ray crystallographic data (CIF) for **6e**; ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) The chemical shift of the olefinic methine carbon in the two possible regioisomers is also diagnostic, δ_C 93.2 for **6e**, in which this carbon is α- to the carbonyl, *cf.* δ_C 106.8 for the other regioisomer, in which this carbon is β- to the carbonyl. See the Supporting Information for spectroscopic data for this regioisomeric product.