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Large-Scale Synthesis of New Pyranoid Building Blocks Based on Aldolase-Catalysed Carbon-Carbon Bond Formation

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Dedicated to Professor Chi-Huey Wong on the occasion of his 60th birthday.

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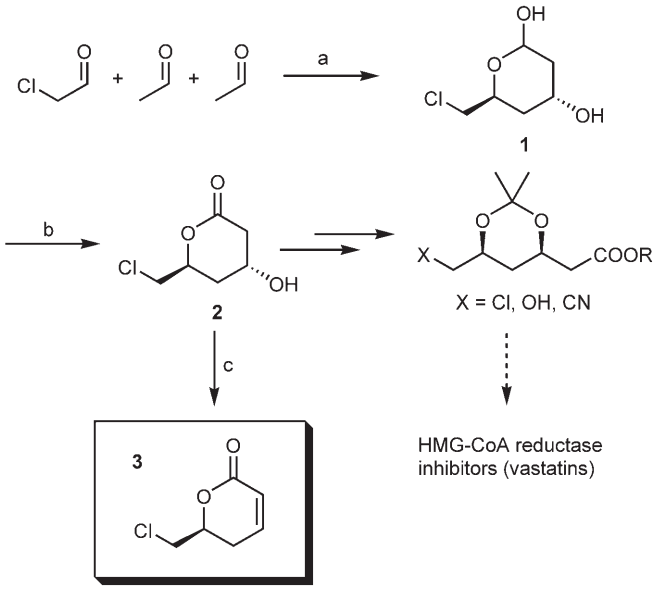
Abstract: A new large-scale approach to the synthetically versatile chloromethyl-substituted, α,β-unsaturated δ-lactone **3** is described. The synthesis is based on a biocatalytic process performed on an industrial scale. Conjugate addition of *C*-, *N*-, *O*-, and *S*-nucleophiles to lactone **3** affords a variety of new pyranoid building blocks in a highly diastereoselective manner. The operational simplicity of the whole sequence allows for preparing these building blocks on an attractive scale.

Keywords: aldolase; conjugate addition; enzymatic catalysis; δ-lactones; large-scale synthesis; α-pyrones

Introduction

Aldolase-catalysed carbon-carbon bond formation is a powerful tool for the construction of complex structures in organic synthesis.[1] The sequential one-pot, two-step aldol addition of two molecules of acetaldehyde to an acceptor aldehyde catalysed by deoxyribose phosphate aldolase (DERA, EC 4.1.2.4), a reaction discovered by Wong and co-workers in 1994,[2] is a particularly intriguing example in this respect. This elegant reaction permits the highly stereoselective construction of 2,4,6-trideoxypyranoses in one operational step, starting from extremely simple small molecule raw materials (Scheme 1, chloroacetaldehyde in the role of the acceptor aldehyde). Chloro trideoxypyranose **1** thus obtained can be oxidised to the crystalline hydroxy lactone **2**, formally a triketide, which can be further elaborated in a few steps to the chiral dihydroxy side chain of HMG CoA reductase inhibitors of the mevinic acid type (vastatins).[3] A scale-up of this route has been realised by some of us recently,[4] including the improvement of the operational stability of the enzyme by directed evolution.[5] Manufac-



Scheme 1. Chemoenzymatic synthesis of lactone **3**. a) DERA, H_2O, pH 7 (refs.[2,4a]); b) Br_2, H_2O, pH 5–6 (ref.[4b]); c) cat. TsOH, toluene, Δ, 84–87%.

turing of hydroxy lactone **2** is operated on an industrial scale at DSM now.

In order to further broaden the applicability of this powerful biocatalytic reaction we investigated the conversion of hydroxy lactone **2** to the α,β-unsaturated δ-lactone **3** (Scheme 1). In view of the susceptibility of β-hydroxy δ-lactones to dehydration, we reasoned that the enantiomerically pure hydroxylactone **2** would serve as a privileged starting material for the preparation of lactone **3**. The α,β-unsaturated δ-lactone is a characteristic structural motif in naturally occurring α-pyrones (5,6-dihydropyran-2-ones), a large family of physiologically active secondary metabolites widely distributed in nature.[6] Apart from this prominent role in nature's molecular architecture, α,β-unsaturated δ-lactones are valuable chiral synthetic intermediates, and building blocks based on this motif have been applied in the total synthesis of natural products and other complex organic molecules frequently. Lactone **3** is of particular value in this respect, since the electrophilic activation of the exocyclic carbon atom leads to a broad synthetic applicability. This has been demonstrated by Enders and coworkers recently who employed lactone **3** and its enantiomer in total syntheses of several naturally occurring α-pyrones.[7]

Apart from the terminal chloro substituent, lactone **3** contains a high density of complemetary functional groups, namely a carbonyl/ester group (C-1), an activated double bond (C-2, C-3), an allylic methylene (C-4), and a (masked) secondary alcohol (C-5) which constitutes a (masked) terminal epoxide together with the chloro substituent (C-5, C-6; carbon chain of all compounds indexed according to the underlying open chain hexanoates throughout this work). Both enantiomers of lactone **3** have been prepared *via* alternative chemoenzymatic routes before.[8] Here, we report about a new large-scale synthesis of lactone **3** and the highly diastereoselective conjugate addition of various nucleophiles to lactone **3**. The products of this reaction are versatile pyranoid building blocks which are of interest for the synthesis of pharmaceuticals and natural products.

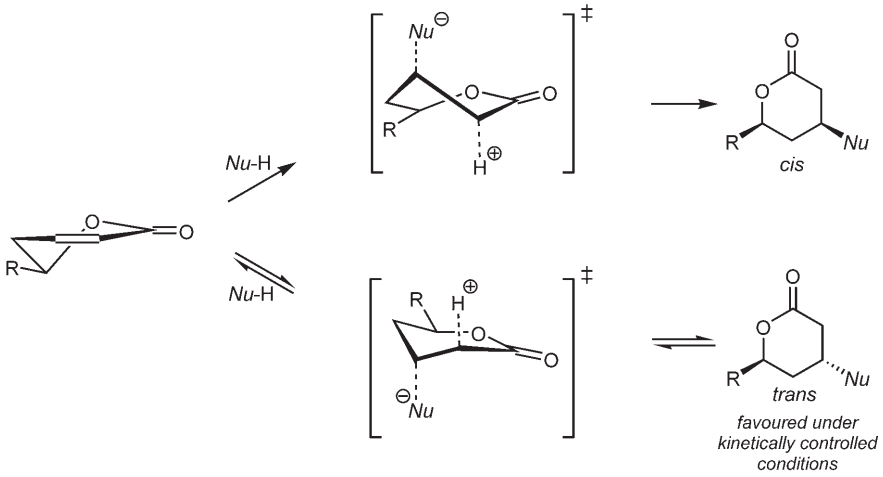
Results and Discussion

The α,β-unsaturated δ-lactone **3** is readily prepared by acid-catalysed dehydration of hydroxy lactone **2** in toluene, aided by azeotropic removal of water (Scheme 1). After a simple aqueous work-up (bicarbonate washing) and evaporation of the solvent in vacuum, lactone **3** is obtained as a yellow oil in 84–87% yield. We performed laboratory batches on 50–100 g scales routinely without problems. Since a few percent toluene (<5%) represents the only significant impurity of the crude product **3**, it can usually be used as such without further purification. If required, lactone **3** can be further purified by vacuum distillation.[9]

Conjugate Addition to Unsaturated Lactone 3

Kinetically controlled conjugate addition to chiral α,β-unsaturated δ-lactones like **3** is well-known to proceed with very high diastereoselectivity in favour of the *trans* configuration. The preference of a chair-like transition state over its less favoured twist-like pendant and stereoelectronic control (axial attack phenomenon) has been invoked to account for this observation (Scheme 2).[10]

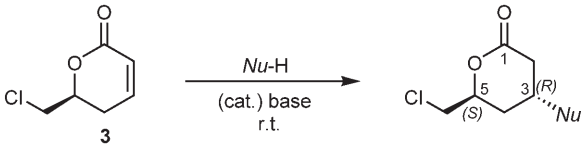
We investigated the base-catalysed conjugate addition of various *C*-, *N*-, *O*-, and *S*-nucleophiles to lac-



Scheme 2. Stereochemical course of the base-catalysed conjugate addition of nucleophiles *Nu*-H to α,β-unsaturated δ-lactones.[10]

tone **3** at ambient temperature (Table 1). Treatment of lactone **3** with thioacetic acid in the presence of a catalytic amount of triethylamine resulted in the highly diastereoselective formation of *S*-acetyl-protected mercapto lactone **4** in 92% yield (*trans*:*cis* 94:6, entry 1). Since lactone **4** has a relatively low melting point (38.2–39.5 °C) and is thus difficult to purify by crystallisation, we turned our attention to the *S*-benzoyl-protected derivative **5**. The addition of thiobenzoic acid to lactone **3** turned out to be slightly less diastereoselective (*trans*:*cis* 92:8, entry 2), but the minor *cis*-isomer was easily removed by a single recrystallisation after which lactone **5** was obtained in 75% yield on a 0.5 mol scale. Conjugate addition of NH-acidic phthalimide to lactone **3** in DMF was sluggish even when a stoichiometric amount of NEt_3 and

Table 1. Conjugate addition of *C*-, *N*-, *O*-, and *S*-nucleophiles (*Nu*-H) to unsaturated lactone **3**.



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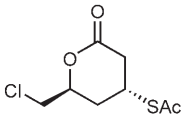
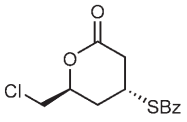
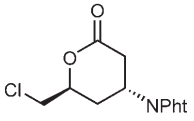
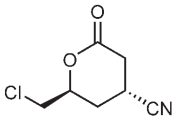
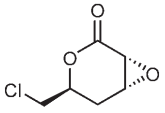
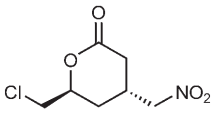
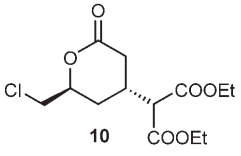
Entry	*Nu*-H[a]	Product	Base [mol equiv]	Solvent	Ratio *trans*:*cis*[b]	Yield [%][c]
1	AcSH	 **4**	NEt_3 (0.03)	MTBE	94:6 (>95:5)[d]	92
2	BzSH	 **5**	NEt_3 (0.02)	MTBE	92:8 (>95:5)[d]	75
3	PhtNH	 **6**	DBU (0.03)	DMF	>95:5	79
4	HCN	 **7**	DBU (0.10)	CH_2Cl_2	>95:5	61
5	*t*-BuOOH	 **8**	DBU (0.25)	toluene	>95:5	60
6	$MeNO_2$	 **9**	DBU (0.10)	(neat)	>95:5	52
7	$CH_2(COOEt)_2$	 **10**	K_2CO_3 (2.0), 18-crown-6 (0.10)	CH_2Cl_2	95:5 (>95:5)[d]	75

[a] Ac = acetyl, Bz = benzoyl, Pht = phthaloyl.
[b] Determined for crude products by NMR spectroscopy.
[c] Yields after recrystallisation or flash chromatography, respectively (except entries 1 and 3: crude product).
[d] Ratio *trans*:*cis* after recrystallisation or column chromatography, respectively.

elevated temperatures were applied. In contrast, application of only 3 mol% DBU as catalyst enabled this reaction to proceed smoothly at ambient temperature and full conversion was reached after stirring overnight. Phthaloyl-protected β-amino lactone **6** precipitates from the reaction mixture and can be isolated in pure form by simple filtration which makes this reaction particularly convenient to be carried out on a large scale (79% yield, 0.5 mol scale, entry 3). We could not detect any traces of the *cis* diastereomer in the crude product. The DBU-catalyzed hydrocyanation of the double bond of lactone **3**, carried out with acetone cyanohydrin as a convenient source of hydrogen cyanide,[11] resulted in smooth and highly diastereoselective formation of secondary nitrile **7** (*trans*:*cis* > 95:5, entry 4). Nitrile **7** was thus obtained in 82% yield after a usual aqueous work-up (61% after recrystallisation). Our initial attempts to use NEt_3 as catalyst for this reaction did not lead to useful conversion which underlines the privileged role of DBU as catalyst for the conjugate additions described here. Epoxidation of lactone **3** was achieved by means of the DBU-catalysed conjugate addition of *tert*-butyl hydroperoxide,[12] again with very high diastereoselectivity (*trans*:*cis* > 95:5, entry 5). Application of azeotropically dried *tert*-butyl hydroperoxide in toluene gave the best results with regard to yield of epoxide **8** and catalyst consumption (25 mol% DBU) in our hands.[13] We found epoxide **8** to be a highly crystalline solid that can be readily purified by recrystallisation (60%, 0.5 mol scale). In contrast, the usual epoxidation with aqueous H_2O_2 in alkaline medium was plagued by significant side-product formation, even when advanced conditions like phase-transfer catalysis in a biphasic system were applied. Attempts to apply the H_2O_2/urea complex in the presence of methyltrioxorhenium for epoxidation of lactone **3** under anhydrous conditions remained fruitless;[14] no conversion could be achieved.

After having evaluated the conjugate addition of heteroatom nucleophiles to lactone **3** we turned our attention to π-stabilised anionic *C*-nucleophiles. Nitromethane was found to add rapidly to lactone **3** in the presence of 10 mol% DBU to afford lactone **9**, virtually as a single diastereomer (*trans*:*cis* > 95:5, entry 6). Application of neat nitromethane in a large excess (20 equiv.) proved to be the most effective conditions. Not unexpectedly,[15] this conjugate addition is hampered by formation of a secondary double addition product which had to be separated from the main product **9** by means of column chromatography.[16] Yield of purified lactone **9** was limited to a moderate 52% under these conditions. Triethylamine and diisopropylethylamine were ineffective in catalysing the addition of nitromethane under identical conditions and only traces of product **9** could be detected after one day reaction time. Conjugate addition of diethyl malonate to lactone **3** was initially attempted using the corresponding lithium enolate preformed with LiH in THF. At low temperature (−10 °C) the reaction was prohibitively slow whereas full conversion could be obtained at ambient temperature after stirring overnight. Lactone **10** was thus obtained in 89% isolated yield. NMR analysis of the crude product indicated the presence of significant amounts of the *cis* diastereomer, however (*trans*:*cis* = 80:20). A similar result was obtained when NaH was used as base whilst application of KO-*t*-Bu gave even worse diastereoselectivity (*trans*:*cis* = 60:40). Better results in terms of diastereoselectivity (*trans*:*cis* = 95:5) were observed with DBU in dichloromethane, but stoichiometric amounts of DBU had to be applied to get full conversion which led to significant formation of decomposition products. We were pleased to see that substitution of solid potassium carbonate under phase-transfer conditions (10 mol% 18-crown-6) for DBU afforded product **10** with equally good diastereoselectivity (*trans*:*cis* = 95:5, entry 7) and as virtually pure crude product. The minor diastereomer was further depleted by means of column chromatography and lactone **10** could be thus obtained analytically pure in 75% yield. Various attempts to bring about a base-catalysed conjugate addition of the cyclic malonic ester derivative Meldrum's acid to lactone **3** failed.

Stereochemical Assignments

Our assignment of the *trans* configuration for all conjugate addition products described here is based on the well-established *trans*-selective stereochemical course of this type of reaction.[10] For the products **4**–**7** this assignment is clearly supported by analysis of the vicinal H,H coupling constants of the hydrogen nuclei attached to the lactone ring (Table 2). The relatively small and almost equal constants $^3J_{H,H}$ of vicinal coupling between H3 and both H2 nuclei (4–7 Hz) as well as between H3 and both H4 nuclei (4–5 Hz) rule out the *cis* configuration for lactones **4**–**7**. In the case of a *cis* configuration H3 would be in pseudo-axial position which would lead to significantly larger *trans* diaxial coupling (9–12 Hz) between H3 and H2′ as well as between H3 and H4′ (Figure 1). The observed values for lactones **4**–**7** correlate with the *trans* configuration in a half-chair conformation where the heteroatom substituent connected to C3 is positioned pseudo-axially and H3 is in a pseudo-equatorial position, thus bisecting the H2−C2−H2′ and the H4−C4−H4′ angles.[17]

The vicinal coupling constants of H3 as observed for the lactones **9** and **10** draw a less clear picture in this respect. Particularly the coupling between H3 and H2′, but also between H3 and H4′, is significantly increased here (10 and 7 Hz, respectively). On the

Table 2. Selected ^{1}H NMR data of the lactones **4–10** (300 MHz, 21 °C, $CDCl_3$).[a]

Cpd. no.	δ (ppm)						$^3J_{H,H}$ (Hz)							
	H2′	H2	H3	H4′	H4	H5	H2,H2′	H2′,H3	H2,H3	H3,H4′	H3,H4	H4,H4′	H4′,H5	H4,H5
4	2.96	2.70[b]	4.07	2.29	2.14[b]	4.74	18	6.5	5.5	5	4.5	14.5	10	4
5	3.06	2.83[b]	4.28	2.39	2.26[b]	4.85	18	6.5	5	5	4	15	10	4.5
6	2.89	3.00	4.70	2.02–2.16		4.77	17.5	7.5	4	n.r.[c]	n.r.	n.r.	n.r.	n.r.
7	2.82	2.90[b]	3.36	2.16	2.30[b]	4.88	18	7	5	5.5	4	14.5	10.5	4
8	3.60	–	3.75	2.22	2.50	4.75	–	4	–	~0.5	3	15	12	3
9	2.42	2.70	2.95	2.15	1.90	4.64	16.5	9.5	6	7	6	14.5	9	4.5
10	2.54	2.66	~2.8	2.12	1.96	4.64	16.5	10.5	5.5	7.5	6.5	14.5	9	4.5

[a] Lactone **6** recorded in DMSO-d_6.
[b] W-coupling observed additionally: $^4J_{H2,H4} = 1.5$ Hz.
[c] n.r. = not resolved.

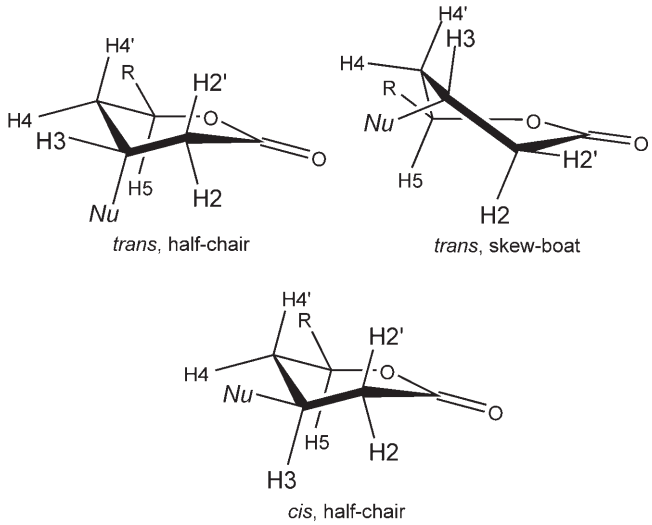


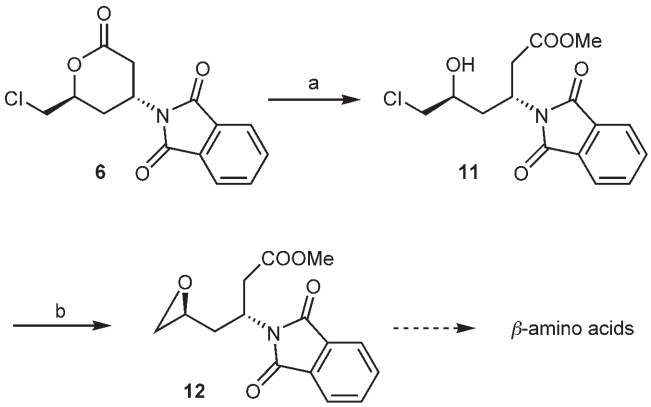
Figure 1. Conformers of 3,5-disubstituted δ-lactones.

other hand, the increase of $^3J_{H3,H4'}$ to 7 Hz is not pronounced enough to support an assignment of a *cis* configuration for which $^3J_{H3,H4'} = 9$–12 Hz would be expected due to *trans* diaxial coupling (see above). Furthermore, an equal or increased value for $^3J_{H4',H5}$ compared to the *trans* cases **4–7** would be expected for the same reason, if lactones **9** and **10** were obtained as *cis* isomers.[18,19] Conversely, a slight decrease of the coupling constant $^3J_{H4',H5}$ from 10 Hz for lactones **4–7** to 9 Hz for lactones **9** and **10** is observed. These observations are indicative for a *trans* configuration with a distortion from the half-chair to a skew-boat conformation which allows for pseude-equatorial positioning of both substituents at C3 and C5 (Figure 1). Such a conformational change can be explained by the fact that the exocyclic tetrasubstituted sp^3 carbon atom of the nitromethyl (lactone **9**) and 2-malonyl (lactone **10**) substituents exerts a higher sterical influence in close proximity to the lactone ring as compared to the heteroatom C3 substituents of the lactones **4–7**. Adoption of a skew-boat conformation has been observed for a similar sterically encumbered 3,5-*trans* δ-lactone in a detailed conformational study before (benzenesulfonyl substituent at C3).[20]

Conformational flexibility is reduced in epoxide **8** because of the constraints imposed by the rigid three-membered ring. The large coupling constant $^3J_{H4',H5}$ of 12 Hz in combination with the clear absence of diaxial coupling between H3 and H4′ strongly supports assignment of the *trans* configuration.

Follow-Up Transformations

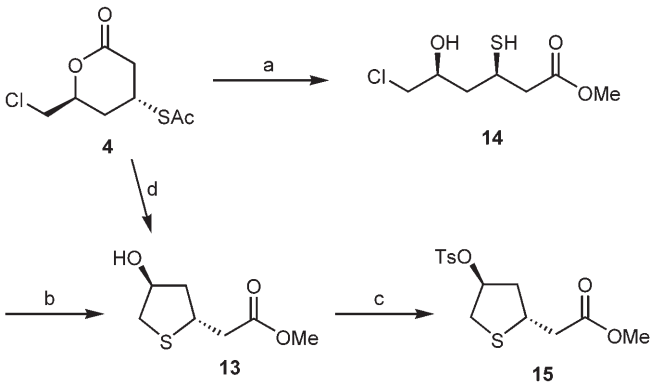
The O–C1 ester bond of *trans*-3,5-disubstituted δ-lactones is readily cleaved by solvolysis to give the corresponding open-chain carboxylic acid derivatives. In the case of the lactones **4–10** this operation unmasks the chlorohydrin moiety which can be dehydrochlorinated to yield a terminal epoxide. Thus, refluxing a suspension of phthaloyl-protected amino lactone **6** in methanol in the presence a catalytical amount of anhydrous HCl for 1.5 h affords methyl hexanoate **11** which we obtained as a highly viscous, clear colourless syrup in quantitative yield (Scheme 3). The reaction



Scheme 3. Synthesis of epoxide **12**. a) cat. HCl, MeOH, Δ, quant.; b) DBU, CH_2Cl_2, 82%; *alternatively:* a,b) K_2CO_3, MeOH, 69%.

can be visually followed by the dissolution of the sparingly soluble lactone **6** as the reaction proceeds. Upon treatment of hexanoate **11** with DBU in dichloromethane the highly crystalline epoxide **12** is obtained (82% yield). Alternatively, epoxide **12** can be obtained in a one-pot tandem reaction when lactone **6** is treated with potassium carbonate in methanol (69% yield). Because of the outstanding synthetic versatility of the terminal epoxide function,[21] we think that epoxide **12** can serve as a useful building block for β-amino acids.

The acetyl-protected mercapto lactone **4** undergoes a more extended tandem reaction when treated with potassium carbonate in MeOH. Ring cleavage is followed by deprotection of the thiol group which subsequently undergoes intramolecular *S*-alkylation, leading to tetrahydrothiophene **13** in a single synthetic step (Scheme 4). NMR and TLC analyses of the



Scheme 4. Synthesis of tosylate **15**. a) cat. HCl, MeOH, quant.; b) DBU, CH_2Cl_2, 65%; c) TsCl, NEt_3, cat. DMAP, CH_2Cl_2, 76%; d) K_2CO_3, MeOH, 53%.

crude product **13** indicated partial epimerisation under these conditions, however. Conversely, a two-step procedure *via* thiol **14**, comprising acid-catalysed methanolysis and deprotection of lactone **4** followed by base induced 5-*exo-tet* ring closure, takes place without affecting the stereochemical integrity of the product **13** (65% yield). Subsequent tosylation of tetrahydrothiophene **13** afforded tosylate **15** in 76% yield after flash chromatography (Scheme 4). Tetrahydrothiophenes similar to **15** have been used as chiral building blocks in the synthesis of modified dideoxy isonucleosides which are under investigation for potential antiviral activity.[22]

Conclusions

In the present work we described a new large-scale synthesis of the synthetically versatile α,β-unsaturated δ-lactone **3**. Key-step of this route is Professor Wong's elegant aldolase-based approach to trideoxypyranose **1**. It has been demonstrated that *C*-, *N*-, *O*-, and *S*-nucleophiles add to the conjugated double bond of lactone **3** with high diastereoselectivity to afford the new *trans*-3,5-disubstituted δ-lactones **4**–**10** in fair to good yields (52–92%). The whole route to lactones **4**–**10** (and further to epoxide **12** and tetrahydrothiophene **15**), starting from the bulk raw materials chloroacetaldehyde and acetaldehyde, is void of low-temperature chemistry, heavy metal catalysts and metalorganic species. The conjugate additions described here have been performed on a scale up to the 100-g range without any difficulties. Due to their favourable set of functional groups, lactone **3** and its derivatives **4**–**15** are attractive building blocks for the synthesis of natural products and pharmaceutically relevant compounds like, e.g., β-amino acids.

Experimental Section

General information and characterisation data of the products **3**–**13** and **15** can be found in the Supporting Information.

Unsaturated Lactone 3

To hydroxy lactone **2** (100 g, 0.61 mol) in toluene (600 mL) was added toluenesulfonic acid monohydrate (3.5 g, 0.02 mol) and the mixture was heated to reflux for 4 h. Reaction water was continously removed by means of a Dean–Stark trap. The batch was cooled to ambient temperature and extracted with saturated aqueous $NaHCO_3$ solution (2× 200 mL) and water (200 mL). The organic phase was concentrated under vacuum and azeotropically dried with toluene once (200 mL). Residual toluene was removed at 50 °C under vacuum (5 mbar) until the weight remained constant. Lactone **3** was thus obtained in form of a yellow oil, virtually pure by ^1H NMR; yield: 78.0 g (87.6%).

Lactone 4

To a solution of unsaturated lactone **3** (73.3 g, 0.50 mol) and NEt_3 (1.7 g, 17 mmol) in MTBE (600 mL) was slowly added thioacetic acid (43.0 g, 0.56 mol), maintaining the temperature at around 20 °C by means of a water bath. The mixture was stirred overnight and washed then, in sequence, with 0.5 M aqueous HCl, 5% aqueous $NaHCO_3$, and brine. The organic phase was dried over Na_2SO_4 and evaporated to dryness under vacuum, leaving lactone **4** as a yellow solid; yield: 103.0 g (92%). A sample was redissolved in MTBE and recrystallised by letting *n*-pentane diffuse into the solution at −18 °C.

Lactone 5

To a solution of unsaturated lactone **3** (73.3 g, 0.50 mol) and NEt_3 (1.3 g, 12 mmol) in MTBE (500 mL) was slowly added thiobenzoic acid (75.1 g, 0.54 mol), maintaining the temperature at around 2–5 °C by means of an ice-water bath. The mixture was stirred at ambient temperature for 5 h, diluted

with ethyl acetate (450 mL) and washed, in sequenece, with 0.5 M aqueous HCl (400 mL), 5% aqueous $NaHCO_3$ (3× 100 mL), and brine. The organic phase was dried over Na_2SO_4 and evaporated to dryness under vacuum, leaving lactone **5** as a weakly orange oil that solidified upon seeding. Recrystallisation from MTBE (500 mL) afforded lactone **5** as an off-white solid; yield: 100.6 g. A second crop (6.3 g) was obtained after concentrating the combined filtrate and washings of the recrystallisation to approx. one half of the original volume; total yield: 75%.

Lactone 6

Phthalimide (73.6 g, 0.50 mol) was dissolved in DMF (340 mL) at 35–40 °C and the solution was cooled to ambient temperature by means of a water bath. Unsaturated lactone **3** (73.3 g, 0.50 mol) and DBU (1.9 g, 12 mmol) were added and the solution was stirred at ambient temperature. After stirring overnight a suspension had formed which was filtered. The filter cake was rinsed with DMF (30 mL) and MTBE (2×50 mL), to afford, after drying at 40 °C under vacuum, spectroscopically pure lactone **6** in the form of heavy, off-white crystals; yield: 115.3 g (79%). A sample was recrystallised from MeCN.

Lactone 7

DBU (1.52 g, 10 mmol) was added to a solution of unsaturated lactone **3** (14.7 g, 0.10 mol) and acetone cyanohydrin (9.4 g, 0.11 mol) in dichloromethane (200 mL) and the solution was stirred at ambient temperature overnight. Saturated aqueous $NaHCO_3$ (100 mL) was added and the mixture was vigorously stirred for 5 min. The aqueous phase was cut and extracted with a few mL of dichloromethane. The combined organic phases were washed, in sequence, with 2 M aqueous HCl (2×50 mL), saturated aqueous $NaHCO_3$ (50 mL), and brine (50 mL). The solution was dried over Na_2SO_4 and evaporated to dryness under vacuum, leaving crude lactone **7** as a brownish syrup that solidified slowly on standing at ambient temperature; yield: 14.2 g (82%). Crude lactone **7** (13.5 g) was dissolved in dichloromethane (41 mL), MTBE was added (50 mL), and the solution was stored at ambient temperature overnight for recrystallisation. The mother liquor was decanted and the crystals washed with chilled (−20 °C) MTBE containing 5 vol% dichloromethane which afforded, after drying under vacuum, lactone **7** in the form of slightly brownish, transparent crystals; yield: 8.1 g, mp 84.5–85.1 °C. A second crop of recrystallised lactone **7** could be obtained from the mother liquor after it was stored at 4 °C overnight (0.5 g, mp 83.9–84.6 °C). Slow evaporation of a part of the new mother liquor by keeping the flask open to the atmosphere in the ventilation hood produced a third crop (1.4 g, mp 84.3–85.2 °C): total yield: 61%.

Lactone 8

An azeotropically dried solution of *tert*-butyl hydroperoxide in toluene (129 mL, 3.4 M, 0.44 mol)[13] was added dropwise to a solution of unsaturated lactone **3** (58.6 g, 0.40 mol) and DBU (15.2 g, 0.1 mol) in toluene (320 mL) within a period of 20 min, maintaining the temperature at 27–35 °C by means of an ice-water bath. The solution was stirred at ambient temperature overnight and quenched by addition of 20% aqueous Na_2SO_3 (100 mL) thereafter. The mixture was stirred for 10 min and 2 M aqueous HCl (40 mL) was added. After separating the phases and extraction of the aqueous phase with toluene (50 mL) the combined organic phases were washed, in sequence, with 2 M HCl (100 mL), half-saturated brine (50 mL), saturated aqueous $NaHCO_3$ (100 mL), and brine (100 mL). The organic phase was dried over Na_2SO_4 and evaporated to dryness under vacuum, leaving crude lactone **8** as an orange oil that solidified spontaneously; yield: 44.6 g (69%). The crude product was dissolved in MTBE (600 mL) at reflux and the solution stored at 4 °C overnight. The precipitate was filtered off, rinsed with chilled TBME (20 mL), and dried under vacuum, yielding lactone **8** in form of off-white crystals; yield: 33.6 g (mp 84.4–85.2 °C). A second crop (4.9 g) was obtained after concentrating the mother liqour to 1/3 of the volume under reduced pressure and storage of the concentrate at 4 °C. Total yield: 60%.

Lactone 9

A solution of DBU (75 μL, 0.5 mmol) in nitromethane (5.6 g, 92 mmol) was cooled in a water bath and unsaturated lactone **3** (0.73 g, 5.0 mmol) was added. After stirring for 5 h at ambient temperature the reaction was quenched by addition of 0.5 M aqueous HCl (10 mL). The mixture was extracted with ethyl acetate (40 mL) and the phases separated. The organic phase was washed with saturated aqueous $NaHCO_3$ (20 mL) and brine (20 mL), dried over Na_2SO_4, and concentrated under vacuum. The viscous residue was subjected to flash chromatography (5 cm Ø column, 100 g silica gel, crude product preadsobed on 6 g silica gel, MTBE as eluent), to afford analytically pure lactone **9** as a clear colourless syrup; yield: 0.54 g (52%).

Lactone 10

To a solution of unsaturated lactone **3** (0.73 g, 5.0 mmol) and dimethyl malonate (0.80 g, 5.0 mmol) in dichloromethane (25 mL) was added powdered K_2CO_3 (1.38 g, 10 mmol) and 18-crown-6 (0.13 g, 0.5 mmol) and the mixture was vigorously stirred for 23 h at ambient temperature. Aqueous HCl (2 M, 20 mL) was added and the phases were seperated. The organic phase was washed with saturated aqueous $NaHCO_3$ (20 mL) and brine (25 mL), dried over Na_2SO_4, and concentrated under vacuum. The oily residue was subjected to flash chromatography (5 cm Ø column, 145 g silica gel, ethyl acetate/*n*-hexane 35:65 v/v as eluent), to afford analytically pure lactone **10** as a clear colourless syrup; yield:. 1.15 g (75%).

Hexanoate 11 and Epoxide 12

To a suspension of lactone **6** (10.0 g, 34 mmol) in methanol (100 mL) was added HCl in 1,4-dioxane (560 μL, 2.7 M, 1.5 mmol) and the mixture was heated to reflux for 1.5 h after which time a clear solution was obtained. Volatiles were removed under vacuum at 50 °C to afford hexanoate **11** as a clear colurless glass; yield: 11.2 g (100%). The crude hexanoate **11** was dissolved in dichloromethane (100 mL) and DBU (7.8 g, 51 mmol) was added. After heating the solution to reflux for 6 h, aqueous HCl (1 M, 100 mL) was added and the phases were separated. The deep brown or-

ganic phase was washed, in sequence, with 0.5 M aqueous HCl (100 mL), 5% aqueous $NaHCO_3$, and brine (100 mL), dried over Na_2SO_4, and filtered through a pad of silica gel. The silica gel pad was rinsed with 50 mL dichloromethane and the combined filtrates evaporated under vacuum, leaving spectroscopically pure epoxide **12** as almost colourless syrup that solidified on standing at ambient temperature; yield: 8.1 g (82%). A sample was recrystallised from MTBE.

Tetrahydrothiophene 13 and Tosylate 15

To a solution of crude (~95%) lactone **4** (0.43 g, 1.8 mmol) in methanol (4 mL) was added HCl in 1,4-dioxane (350 μL, 2.7 M, 0.9 mmol) and the solution was stirred at ambient temperature for three days. Volatiles were removed under vacuum to afford thiol **14** as a yellow oil in near quantitative yield (0.38 g). The residue was taken up in dichloromethane (8 mL), cooled in an ice-water bath, and DBU (300 μL, 2.0 mmol) was added dropwise over a period of 2 min. The ice-bath was removed and the solution was stirred for 2 h at ambient temperature. The solution was washed, in sequence, with 2 M HCl, saturated aqueous $NaHCO_3$, and brine, dried over Na_2SO_4, and concentrated under vacuum. The oily residue (0.27 g) was subjected to flash chromatography (3 cm Ø column,100 mL silica gel, ethyl acetate/*n*-hexane 55:45 v/v as eluent), to afford tetrahydrothiophene **13** as a clear colourless oil; yield: 0.21 g (65%). To a solution of tetrahydrothiophene **13** thus obtained (0.21 g, 1.2 mmol) in dichloromethane (~5 mL) was added NEt_3 (180 μL g, 1.3 mmol) and tosyl chloride (0.23 g, 1.2 mmol) and the mixture was stirred at ambient temperature for 20 h. Since TLC analysis indicated incomplete conversion at this point, DMAP (16 mg, 0.1 mmol) and another portion of tosyl chloride (19 mg, 0.1 mmol) and NEt_3 (90 μL, 0.6 mmol) were added and stirring was continued for one week. Ethyl acetate (40 mL) was added and the solution was washed, in sequence, with 2 M HCl, saturated aqueous $NaHCO_3$, and brine, dried over Na_2SO_4, and concentrated under vacuum. The viscouse residue (0.33 g) was subjected to flash chromatography (2 cm Ø column, 60 mL silica gel, ethyl acetate/*n*-hexane 35:65 v/v as eluent), to afford tosylate **15** as a pale yellow syrup; yield: 0.30 g (76%).

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