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TETRAHEDRON: *ASYMMETRY*

Selective conjugate addition of nitromethane to enoates derived from D-mannitol and L-tartaric acid

Américo C. Pinto,[a] Cleide B. L. Freitas,[a] Ayres G. Dias,[c] Vera L. P. Pereira,[b,*] Bernard Tinant,[d] Jean-Paul Declercq[d] and Paulo R. R. Costa[a,*]

[a]*Laboratório de Química Bioorgânica (LQB), Núcleo de Pesquisas de Produtos Naturais, Centro de Ciências da Saúde, Bloco H, Ilha da Cidade Universitária, Universidade Federal do Rio de Janeiro, 21941-590, Rio de Janeiro, Brazil*

[b]*Laboratório de Síntese Estereosseletiva de Substâncias Bioativas (LASESB), Núcleo de Pesquisas de Produtos Naturais, Centro de Ciências da Saúde, Bloco H, Ilha da Cidade Universitária, Universidade Federal do Rio de Janeiro, 21941-590, Rio de Janeiro, Brazil*

[c]*Instituto de Química, Universidade do Estado do Rio de Janeiro, Rio de Janeiro, Brazil*

[d]*Laboratorie de Chimie Physique et de Cristallographie, Université Catholique de Louvain, 1, Place Pasteur, 1348 Louvain-la-Neuve, Belgium*

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Abstract—The conjugate addition of nitromethane to enoates prepared from D-(+)-mannitol, substituted at the α-position by a methyl or a benzyl group, was investigated. While excellent *syn*-selectivity (d.e. >90%) was obtained from α-benzyl enoates (used as a mixture of epimers, $E/Z = 1.8:1$), for α-methyl enoates the selectivity depended on the stereochemistry of the double bond in the acceptor (d.e. >90% for the (*Z*)-enoate and 50% for the (*E*)-enoate). In all cases, a mixture of epimers was formed at the newly generated stereocenter at the α-position. The epimeric *syn*-adducts were transformed into the corresponding pure α,β,γ-trisubstituted γ-butyrolactones by cyclization in acid medium followed by epimerization of the stereocenter at the α-position in DBU/CH_2Cl_2. When enoates derived from L-tartaric acid were used as acceptors, *syn*-selective conjugate additions were also observed (d.e. >90% for the (*Z*)-isomer and 50% for the (*E*)-isomer). The configuration at the newly generated stereogenic centers were assigned based on X-ray analyses, ^1H–^1H coupling constants and NOE experiments in NMR spectroscopy.

1. Introduction

Enoates such as (*S*)-**1**, prepared in three steps from D-(+)-mannitol, have been extensively used as acceptors in stereoselective conjugate additions[1] (Fig. 1). The reaction of these enoates with nitromethane and derivatives in the presence of TBAF or DBU was recently described by our group.[2a] *syn*-Adducts were obtained stereoselectively in these conjugate additions and the best stereoselectivities (d.e. >90% at C(3)) were achieved from (*Z*)-enoates. Herein, we disclose the results obtained when enoates (*S*)-**2a** and **2b**, substituted at the α-position by a methyl and a benzyl group, respectively, were used as acceptors.[3] The conjugate addition of

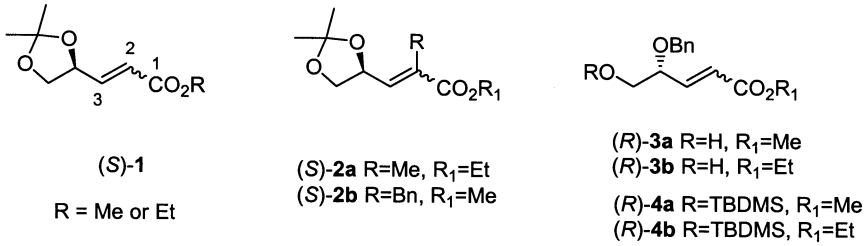

Figure 1.

* Corresponding authors. E-mail: lqb@nppn.ufrj.br

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nitromethane and derivatives to enoates (*R*)-**3a**,**b** and (*R*)-**4a**,**b**, that are prepared from L-(+)-tartaric acid[4] and represent a potential source of adducts with an enantiomeric relationship at the C(3) stereogenic center, was also investigated.

2. Results and discussion

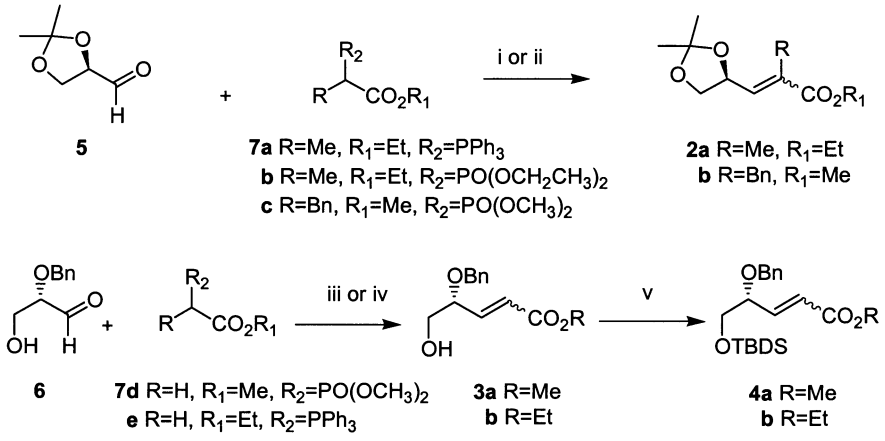
Aldehydes **5** and **6**, easily prepared from D-(+)-mannitol[5] and L-(+)-tartaric acid,[4] respectively, were used as precursors of enoates **2** and **3** (Scheme 1). Compound (*E*)-**2a** was stereoselectively obtained by reaction of **5** with phosphorane **7a**. On the other hand, a mixture of (*Z*)- and (*E*)-**2a** (*Z*/*E*=1.3:1.0), easily separated by chromatography, was prepared by reacting **5** with phosphonate **7b**.[6] However, reaction of **6** with phosphonate **7c**[6] led to an inseparable mixture of (*Z*)- and (*E*)-**2b** (*E*:*Z*=1.8:1.0). The reaction of **6** with phosphonate **7d** led exclusively to (*E*)-**3a** and this adduct was transformed in the *O*-silyl derivative (*E*)-**4a** by reaction with TBDMSCl. On the other hand, the reaction of **6** with phosphorane **7e** at 0°C led to a mixture of (*Z*)- and (*E*)-**3b** (*Z*:*E*=3:1). This mixture was allowed to react with TBDMSCl leading to a corresponding mixture of (*Z*)- and (*E*)-**4b** (*Z*:*E*=3:1).

Scheme 2 shows the results obtained in the conjugate addition of nitromethane **8** to enoates **2a** and **2b**.[7] When (*Z*)-**2a** was used as acceptor, a mixture of two easily separable *syn*-adducts **9a** and **10a**, epimeric at the α-stereocenter, was formed (Table 1, entry 1). Analysis of the ^{13}C NMR spectra of each isolated product showed the presence of only one stereoisomer as the result of a highly selective *syn*-conjugate addition at C(3) (d.e. at C(3) >90%). This mixture of epimers was also formed from enoate (*E*)-**2a**, but in this case ^{13}C NMR spectra showed that these compounds were obtained in lower d.e. at C(3) (50% for both products, entries 2 and 3). In contrast with these results, the addition to enoate **2b**, used as a mixture of geometric isomers (*E*/*Z*=1.8/1.0), led to a mixture of *syn*-adducts **9b** and **10b**, which are epimers at the α-stereocenter, in excellent d.e. at C(3) for each product (>90%). Thus, for this enoate the stereoselectivity is not affected by the geometry of the double bond.

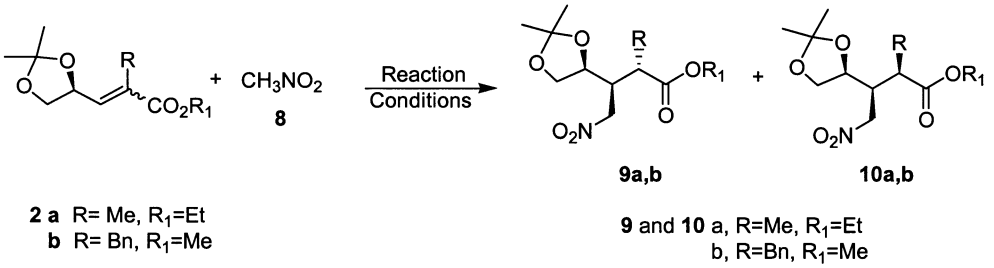
Table 1.

Entry	Enoate	Conditions[b]	Yield (%)	*syn*/*anti* (d.e.)[c]
1	(*Z*)-**2a**	TBAF/1 equiv./4 h	76	>90
2	(*E*)-**2a**	TBAF/1 equiv./20 h	54	50
3	(*E*)-**2a**	TBAF/1 equiv./7 h	56	50
4	**2b**[a]	TBAF/0.5 equiv./20 h	75	80
5	**2b**	TBAF/1 equiv./12 h	65	80
6	**2b**	TBAF/1 equiv./20 h	93	80
7	**2b**	DBU/1 equiv./4 days	41	>90

[a] Used as a mixture of *E*/*Z*-isomers (1.8:1.0).
[b] All reactions were completed at rt and the base/solvent systems used were TBAF/THF or DBU/CH_3CN.
[c] Measured by quantitative ^{13}C NMR.



Scheme 1. *Reagents and conditions*: (i) MeOH, 2 h, **7a**, 0°C (68%), *E*-**2a**; (ii) NaH, THF, 1 h, **7b**, –78°C to rt (61%), 1.0:1.3 *E*:*Z*-**2a**, and **7c** (68%), 1.8:1.0 *E*:*Z*-**2b**; (iii) NaH, THF, 1 h, **7d**, –78°C to rt (81%), *E*-**3a**; (iv) MeOH, 1 h, **7e**, 0°C (70%), 3:1 *Z*:*E*-**3b**; (v) TBDMSCl, imidazol, CH_2Cl_2, 10 h, rt (82%).



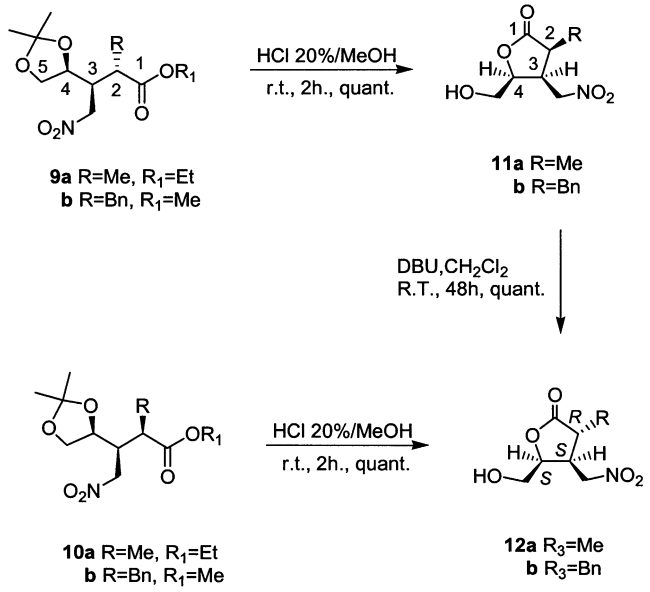
Scheme 2.

Unfortunately, the enoates alkylated at the α-position are less reactive than (*S*)-**1** and adducts were not obtained when nitroethane and 2-nitropropane were used as nucleophiles under the conditions employed.

The adducts **9a** and **10a** were separated by column chromatography and the absolute configuration at the newly generated stereogenic centers were determined through their transformation into the corresponding lactones **11a** and **12a**, respectively (Scheme 3). X-Ray crystallographic analysis of lactone **11a** (Fig. 2)[8] confirmed the *cis–cis* relationship of the substituents and, as a consequence, the 2*S*,3*S*-stereochemistry of adduct **9a**. The lactone **11a** was promptly transformed into its thermodynamic epimer **12a** by treatment with DBU. In this manner, the stereochemistry of **9b** was assigned as 2*R*,3*S*. The mixture of adducts **9b** and **10b** were lactonized and subsequently separated into the lactones **11b** and **12b**. A *trans–cis* relationship in **12b** was determined by X-ray crystallographic analysis (Fig. 2)[9] and this compound was also obtained from the epimeric lactone **11b**, by reaction with DBU.

Scheme 4 shows the addition of nitromethane derivatives to (*R*)-enoates **3** and **4**. When (*E*)-**3a** was allowed to react with nitromethane **8** in the presence of TBAF/THF or DBU/CH_3CN only starting material was recovered (Table 2, entries 1 and 2). However, the corresponding *O*-silyl enoates **4** reacted with **8** in both reaction conditions, leading to the corresponding *syn*-adduct **13**. While very good stereoselectivity was observed in the reactions of (*Z*)-**4b** (d.e. = 90%, entries 3 and 4), moderate stereoselectivity was observed in the additions to (*E*)-**4a** (d.e. = 52%, entries 4–7). Similarly to that observed for enoates **2a** and **2b**, enoates **4a** and **4b** did not react with nitroethane and 2-nitropropane.

In order to establish unambiguously the stereochemistry at the newly generated stereogenic center of **13**, this adduct was transformed into the lactone **14**



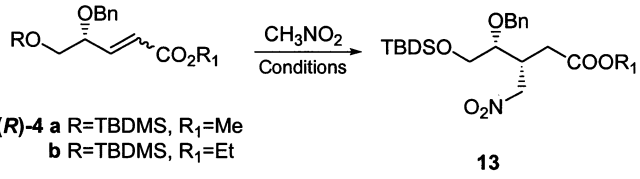
9a R=Me, R_1=Et
b R=Bn, R_1=Me

11a R=Me
b R=Bn

10a R=Me, R_1=Et
b R=Bn, R_1=Me

12a R_3=Me
b R_3=Bn

Scheme 3.



(*R*)-4 a R=TBDMS, R_1=Me
b R=TBDMS, R_1=Et

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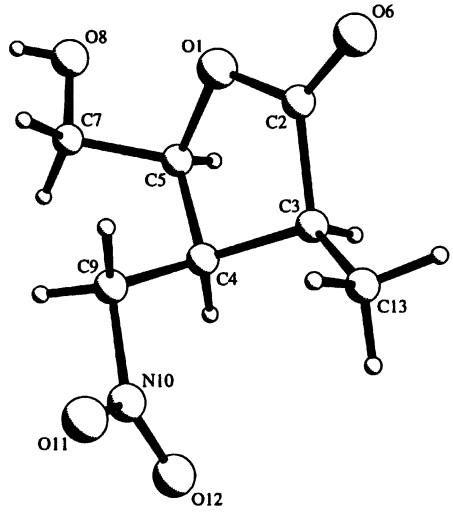
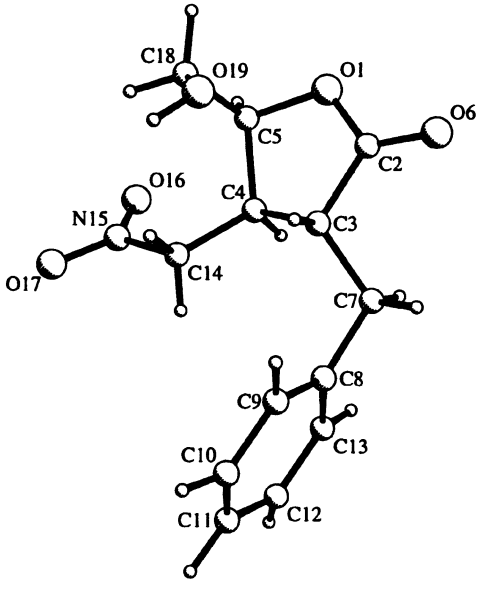
Scheme 4.



11a



12b

Figure 2.

Table 2.

Entry	Enoate	Conditions[a]	Yield (%)	D.e. (%)[b]
1	(*E*)-**3**[a]	TBAF/8 h/34°C[c]	–	–
2	(*Z*)- or (*E*)-**3b**	DBU/8 h/34°C	–	–
3	(*Z*)-**4b**[d]	TBAF/8 h/34°C	65	90
4	(*Z*)-**4b**	DBU/8 h/34°C	64	90
5	(*E*)-**4b**	TBAF/8 h/34°C	70	52
6	(*E*)-**4**[a]	TBAF/12 h/35°C	65	52
7	(*E*)-**4**[a]	DBU/8 h/34°C	64	52

[a] The reactions used TBAF/THF or DBU/CH_3CN as a base/solvent system.
[b] Measured by quantitative ^{13}C NMR.
[c] Room temperature observed was 34°C.
[d] Enoate (*Z*)-**4b** was used with an enriched mixture (86:14, *Z*:*E*) after flash column chromatography.

(Scheme 5). The *trans*-relationship between the substituents at C(3) and C(4) was suggested by the coupling constant between the C(3) and C(4) protons ($J=7.1$ Hz) in the ^1H NMR spectra, and this relationship could be confirmed by the absence of any NOE effect at C(3) after irradiation at C(4).[10]

3. Experimental

3.1. Materials

All conjugate additions were performed under N_2 atmosphere. THF was distilled from sodium benzophenone under N_2 and DMF from CaH_2. Acetonitrile was dried over molecular sieves 4 Å. TBAF·$3H_2O$ solid, nitroethane, MeOH, benzene, 2-nitropropane, HCl (37%), TBDMSCl and imidazole were commercially available (Aldrich, Fluka or Merck) and were used as purchased. The enoates, **2a**,**b** and **3a**,**b**, were prepared according to literature procedures.[2] ^1H and ^{13}C NMR spectra were recorded on a Varian Gemini-200 (200 MHz) instrument in $CDCl_3$ unless specified otherwise. The coupling constant (*J*) is in hertz (Hz). HPLC analyses were performed on a Shimadzu LC-A10 chromatograph using a Shimadzu column C_{18} (25×1.6 cm, ID×5 μm). High-resolution mass spectra were recorded on Micromass $MM_{12}F$ and VG AutoSpec spectrometers. IR spectra were recorded on a Perkin–Elmer model 783 spectrophotometer and optical rotations were measured on a Perkin–Elmer model 243-B polarimeter. All melting points are uncorrected and were determined on a Thomas Hoover apparatus.

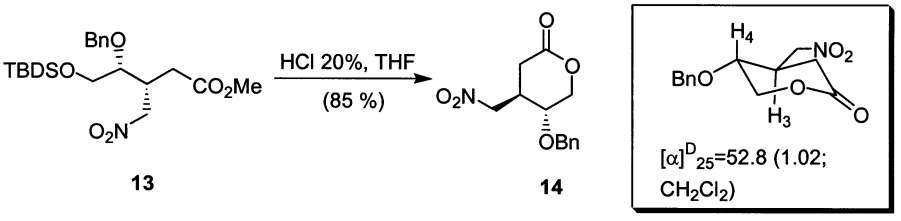
3.2. General procedure for the preparation of enoates

3.2.1. Procedure A—using phosphonate. To a stirred suspension of NaH (0.50 g, 21.0 mmol) in anhydrous THF (50 mL) at rt, was added dropwise **7b** (0.50 g, 1 mmol). After 0.5 h the mixture was cooled at −78°C and D-(+)-glyceraldehyde **5** (3.28 g, 25.1 mol) was added dropwise and the mixture was stirred, allowing to warm to rt. After 1 h, saturated aqueous NH_4Cl solution (30 mL) was added. The organic layer was removed in vacuum and the residual oil was dissolved with AcOEt (120 mL) and washed with saturated solution of K_2CO_3 (45 mL), brine (2×45 mL). The organic phase was dried with $MgSO_4$, filtered and the solvent was removed in vacuum. The residue was purified by flash column chromatography on silica gel (AcOEt:Hex., 15:85) furnished **2a**, as a colorless oil (2.76 g, 61%) (*E*:*Z*, 1:1.3). Analytical samples were obtained by flash column chromatography on silica gel (AcOEt:Hex., 5:95).

3.2.2. Procedure B—using phosphorane. The phosphorane **7e** (0.97 g, 2.78 mmol) was added to a solution of (*S*)-2-*O*-benzyloxyglyceraldehyde **6** (0.50 g, 2.78 mmol) in methanol (2 mL) cooled to 0°C. The mixture was stirred at 0°C for 1 h and the solvent was removed in vacuum. The residue was extracted with hot hexane, the solvent was removed in vacuum to give a white oil, which was purified by flash chromatography on silica gel eluted with hexane to give **3b** as a yellow oil (0.41 g, 60%; ratio *Z*:*E*, 76:24). The isomers were separated by preparative plate chromatography.

3.2.2.1. Ethyl (4*S*)-2-methyl-4,5-*O*-isopropylidene-*cis*-2-pentenoate, (*Z*)-2a. Colorless oil; $[\alpha]_D^{25}=+66.3$ (*c* 1.02, $CHCl_3$), lit. $[\alpha]_D^{25}=+64.6$ (*c* 1.02, $CHCl_3$);[11] ^1H NMR (200 MHz, $CDCl_3$) δ (ppm): 1.31 (t, 3H, $J=7.1$ Hz), 1.38 (s, 3H), 1.45 (s, 3H), 1.93 (d, 3H, $J=1.4$ Hz), 3.59 (dd, 1H, $J=8.2$ Hz, $J=6.9$ Hz), 4.20 (q, 2H, $J=7.1$ Hz), 4.31 (dd, 1H, $J=9.2$ Hz, $J=6.7$ Hz), 5.27 (ddd, 1H, $J=6.9$ Hz, $J=6.9$ Hz, $J=6.7$ Hz), 6.07 (dq, 1H, $J=6.9$ Hz, $J=1.4$ Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm): 13.9 (CH_3), 19.6 (CH_3), 25.2 (CH_3), 26.3 (CH_3), 60.3 (CH_2), 69.3 (CH_2), 73.7 (CH), 109.0 (C), 129.0 (CH_2), 142.0 (CH), 166.6 (C); MS (70 eV) *m*/*z* (%): 213 (2.4), 199 (11.2), 111 (100), 98 (75.8), 83 (61.5), 72 (77.0), 55 (31).

3.2.2.2. Ethyl (4*S*)-2-methyl-4,5-*O*-isopropylidene-*trans*-2-pentenoate, (*E*)-2a. Colorless oil; $[\alpha]_D^{25}=+17.6$ (*c* 1.25, $CHCl_3$). lit. $[\alpha]_D^{25}=+16.4$ (*c* 1.01, $CHCl_3$);[11] ^1H NMR (200 MHz, $CDCl_3$) δ (ppm): 1.30 (t, 3H, $J=7.1$



13 14

Scheme 5.

Hz), 1.41 (s, 3H), 1.46 (s, 3H), 1.90 (d, 3H, $J=1.5$ Hz), 3.63 (dd, 1H, $J=8.2$ Hz, $J=7.6$ Hz), 4.16 (dd, 2H, $J=8.2$ Hz, $J=6.2$ Hz), 4.21 (q, 2H, $J=7.0$ Hz), 4.87 (ddd, 1H, $J=6.2$ Hz, $J=6.6$ Hz, $J=7.6$ Hz), 6.65 (dq, 1H, $J=6.6$ Hz, $J=1.5$ Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm): 12.7 (CH_3), 13.9 (CH_3), 25.6 (CH_3), 26.3 (CH_3), 60.6 (CH_2), 68.5 (CH_2), 72.5 (CH), 109.5 (C), 130.8 (C), 137.9 (CH), 167.0 (C); MS (70 eV) m/z (%): 213 (2.4), 199 (11.2), 111 (66.4), 98 (45.3), 83 (42.5), 72 (100.0), 55 (37.3).

3.2.2.3. Methyl (4*S*)-2-benzyl-4,5-*O*-isopropylidene-*trans*-2-pentenoate, (*E*)-2b. (Maj.); ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm): 1.40 (s, 3H), 1.45 (s, 3H), 3.55–3.64 (m, 1H), 3.72 (s, 3H), 3.83 (d, 1H, $J=15.1$ Hz), 4.00 (dd, 1H, $J=8.2$ Hz, $J=6.3$ Hz), 4.92 (ddd, 1H, $J=8.5$ Hz, $J=7.5$ Hz, $J=6.3$ Hz), 6.85 (d, 1H, $J=8.5$ Hz), 7.10–7.40 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm): 25.4 (CH_3), 26.2 (CH_3), 32.3 (CH_2), 51.6 (CH_3), 68.3 (CH_2), 72.2 (CH), 109.6 (C), 125.9 (CH), 127.7 (2CH), 128.1 (2CH), 133.4 (C), 138.6 (CH), 139.6 (CH), 166.8 (C); MS (70 eV) m/z (%): 276 (1.2), 218 (71.4), 91 (93.2), 72 (100).

3.2.2.4. Methyl (4*S*)-2-benzyl-4,5-*O*-isopropylidene-*cis*-2-pentenoate, (*Z*)-2b. (Min.); ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm): 1.38 (s, 3H), 1.42 (s, 3H), 3.55–3.64 (m, 1H), 3.69 (s, 3H), 4.32 (dd, 1H, $J=8.2$ Hz, $J=6.3$ Hz), 5.26 (d, 1H, $J=6.9$ Hz, $J=6.8$ Hz, $J=6.8$ Hz), 6.08 (dt, 1H, $J=6.9$, $J=1.2$ Hz), 7.10–7.40 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm): 25.1 (CH_3), 26.2 (CH_3), 39.2 (CH_2), 51.3 (CH_3), 69.3 (CH_2), 73.8 (CH), 109.1 (C), 126.1 (CH), 128.1 (2CH), 128.3 (2CH), 132.4 (C), 138.1 (C), 143.3 (CH), 166.4.

3.2.2.5. Methyl (4*R*)-benzyloxy-5-hydroxy-*trans*-2-pentenoate, (*E*)-3a. Colorless oil; $[\alpha]_D^{25}=-45.5$ (c 2.2, CH_2Cl_2); ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm): 1.30 (t, 3H, $J=7.1$Hz), 3.59 (dd, 1H, $J=11.7$ Hz, $J=6.8$ Hz), 3.69 (dd, 1H, $J=11.7$, $J=3.9$ Hz), 4.15 (m, 1H), 4.22 (q, 2H, $J=7.1$ Hz), 4.43 (d, 1H, $J=11.6$ Hz), 4.67 (d, 1H, $J=11.6$ Hz), 6.12 (dd, 1H, $J=15.8$, $J=1.3$ Hz), 6.85 (dd, 1H, $J=15.8$ Hz, $J=6.1$ Hz), 7.25–7.45 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm): 51.5 (CH_3), 64.3 (CH_2), 71.3 (CH_2), 78.8 (CH), 123.2 (CH), 127.7–128.3 (CH), 137.3 (C), 144.5 (CH), 166.1 (C).

3.2.2.6. Ethyl (4*R*)-benzyloxy-5-hydroxy-*cis*-2-pentenoate, (*Z*)-3b. Colorless oil; $[\alpha]_D^{25}=-74.4$ (c 0.40, CH_2Cl_2); ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm): 1.20 (t, 3H, $J=7.0$ Hz), 2.10 (s, 1H), 3.62 (dd, 1H, $J=5.2$ Hz), 3.72 (dd, 1H, $J=4.4$ Hz), 4.16 (q, 2H, $J=7.0$ Hz), 4.46 (d, 1H, $J=11.5$ Hz), 4.58 (d, 1H, $J=11.5$ Hz), 5.1 (m, 1H), 5.96 (dd, 1H, $J=11.8$ Hz, $J=1.28$ Hz), 6.22 (dd, 1H, $J=11.8$ Hz, $J=8.15$ Hz), 7.3 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm): 14.0 (CH_3), 60.4 (CH_2), 64.5 (CH_2), 71.3 (CH_2), 76.3 (CH), 122.9 (CH), 127.4–128.5 (C), 137.7 (C), 147.3 (CH), 165.7 (C).

3.3. Representative procedure for *O*-silylation

To a solution of enoate (*E*)-**3a** (0.86 g, 3.64 mmol) in CH_2Cl_2 (6 mL) at 0°C was added TBDMSCl (0.63 g, 4.19 mmol) in CH_2Cl_2 (3 mL) and imidazole (0.28 g, 4.19 mmol) in CH_2Cl_2 (2 mL) and the mixture was stirred at rt for 12 h. The reaction mixture was dissolved in AcOEt, the resulting solution was washed with 5% aqueous HCl (30 mL), saturated $NaHCO_3$ (30 mL) and the organic phase was dried over anhydrous Na_2SO_4. The solvent was removed in vacuum and the residue was purified by column chromatography on silica gel (Hex./AcOEt 98:2) yielding methyl (4*R*)-benzyloxy-5-*tert*-butyldimethylsilanoxy-*trans*-2-pentenoate (*E*)-**4a** as an oil (1.02 g, 80%); $[\alpha]_D^{25}=-3.9$ (c 2.2, CH_2Cl_2); ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm): 0.00 (s, 6H), 0.90 (s, 9H), 3.64 (dd, 1H, $J=10.4$ Hz, $J=5.6$ Hz), 3.75 (dd, 1H, $J=10.4$ Hz, $J=6.3$ Hz), 3.76 (s, 3H), 4.10 (m, 1H), 4.55 (d, 1H, $J=12.0$ Hz), 4.67 (d, 1H, $J=12.0$ Hz), 6.12 (dd, 1H, $J=16.0$ Hz, $J=1.0$ Hz), 6.92 (dd, 1H, $J=16.0$ Hz, $J=6.0$ Hz), 7.35 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm): −5.5 (CH_3), −5.6 (CH_3), 18.1 (C), 25.7 ($3CH_3$), 51.5 (CH_3), 65.4 (CH_2), 71.5 (CH_2), 78.8 (CH_2), 122.3 (CH), 127.5–128.2 (CH), 137.9 (C), 145.9 (CH), 166.4 (C); MS (70 eV) m/z (%): 73 (21), 91 (100), 293 (6).

3.3.1.1. Ethyl (4*R*)-benzyloxy-5-*tert*-butyldimethylsilanoxy-*cis*-2-pentenoate, (*Z*)-4b. Oil; $[\alpha]_D^{25}=-3.6$ (c 1.1, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm): 0.08 (s, 6H), 0.80 (s, 9H), 1.25 (t, 3H, $J=7.0$ Hz), 3.70 (dd, 1H, $J=10.4$ Hz, $J=5.6$ Hz), 4.45 (q, 2H, $J=7.0$ Hz), 4.50 (d, 1H, $J=12.0$ Hz), 4.52 (d, 1H, $J=12.0$ Hz), 5.10 (m, 1H), 5.90 (dd, 1H, $J=11.8$ Hz, $J=1.0$ Hz), 6.25 (dd, 1H, $J=11.8$ Hz, $J=8.4$ Hz), 7.30 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm): −5.4 (CH_3), 14.1 (CH_3), 18.2 (C), 25.8 ($3CH_3$), 60.1 (CH_2), 65.4 (CH_2), 71.4 (CH_2), 76.1 (CH), 122.3 (CH), 138.4 (C), 147.6 (CH), 165.0 (C); MS (70 eV) m/z (%): 73 (26), 91 (100), 149 (11).

3.4. General procedures for the addition of nitromethane

3.4.1. Procedure A—TBAF as base. A solution of TBAF·$3H_2O$ (0.14 g, 0.55 mmol) in THF (2 mL) was added to a mixture of enoate **2b** (0.30 g, 1.10 mmol), nitromethane (0.067 g, 1.10 mmol) in THF (3 mL). The mixture was stirred at rt for 10 h then washed with H_2O (10 mL), extracted with CH_2Cl_2 (3×15 mL), the organic phase was dried over Na_2SO_4 and the solvent was removed in vacuum. The residue was purified by flash column chromatography on silica gel (Hex.:AcOEt 90:10) yielding a mixture of **9b** and **10b** as an oil (0.27 g, 72%; *syn*:*anti*, 9:1 at C(3)/C(4) and 54:46 at C(2)).

3.4.2. Procedure B—DBU as base. A solution of (*Z*)-**4b** (0.20 g, 0.55 mmol) and nitromethane (0.03 g, 0.55 mmol) in 2 mL CH_3CN was added DBU (0.08 mL, 0.55 mmol). The mixture was stirred at rt for 8 h, then washed with H_2O (2 mL) and 5% aqueous HCl solution was added dropwise until the mixture had a pH of 7 (12 to other adducts). The resulting solution was extracted with AcOEt (3×10 mL). The organic phases were dried

over Na_2SO_4 and the solvent was removed in vacuum. The residue was purified by column chromatography on silica gel (Hex.:AcOEt 95:5) yielding adduct **13** (0.15 g, 64%).

3.4.2.1. Ethyl (2*S*,3*S*,4*S*)-2-methyl-3-nitromethyl-4,5-*O*-isopropylidenepentanoate, 9a. Colorless oil; $[\alpha]_D^{25}=+13.3$ (*c* 1.35, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm): 1.27 (t, 3H, $J=7.1$ Hz), 1.27 (d, 3H, $J=7.2$ Hz), 1.31 (s, 3H), 1.37 (s, 3H), 2.63 (dq, 1H, $J=7.2$, $J=4.8$ Hz), 2.73–2.84 (m, 1H), 3.70 (ddd, 2H, $J=11.6$ Hz, $J=6.0$ Hz, $J=3.9$ Hz), 4.15 (q, 2H, $J=7.1$ Hz), 4.54 (dd, 1H, $J=14.1$ Hz, $J=6.0$ Hz), 4.63 (dd, 1H, $J=14.1$ Hz, $J=5.4$ Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm): 13.9 (CH_3), 14.1 (CH_3), 24.9 (CH_3), 25.9 (CH_3), 39.5 (CH), 43.0 (CH), 60.9 (CH_2), 67.8 (CH_2), 74.0 (CH_2), 74.9 (CH), 109.4 (C), 173.6 (C).

3.4.2.2. Ethyl (2*R*,3*S*,4*S*)-2-methyl-3-nitromethyl-4,5-*O*-isopropylidenepentanoate, 10a. Colorless oil; $[\alpha]_D^{25}=-7.0$ (*c* 1.48, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm): 1.20 (d, 3H, $J=7.2$ Hz), 1.28 (t, 3H, $J=7.1$ Hz), 1.31 (d, 3H, $J=0.5$ Hz), 1.38 (d, 3H, $J=0.5$ Hz), 2.63 (dq, 1H, $J=7.2$, $J=5.0$ Hz), 2.77–2.88 (m, 1H), 3.66–3.77 (m, 1H), 4.08–4.21 (m, 2H), 4.16 (q, 2H, $J=7.1$ Hz), 4.58 (d, 2H, $J=5.8$ Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm): 13.6 (CH_3), 13.9 (CH_3), 25.8 (CH_3), 25.9 (CH_3), 39.8 (CH), 42.7 (CH), 61.0 (CH_2), 68.0 (CH_2), 73.8 (CH_2), 75.0 (CH), 109.4 (C), 173.7 (C).

3.4.2.3. Ethyl (3*R*,4*R*)-3-nitromethyl-4-benzyloxy-5-*tert*-butyldimethylsilanoxypentanoate, 13. Yellow oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm): 0.06 (s, 6H), 0.89 (s, 9H), 1.25 (t, 3H, $J=7.2$ Hz), 2.45 (dd, 1H, $J=16.5$ Hz, $J=6.8$ Hz), 2.62 (dd, 1H, $J=16.5$ Hz, $J=6.8$ Hz), 3.03 (m, 1H), 3.60 (dd, 2H, $J=10.1$ Hz, $J=4.5$ Hz), 3.75 (sl, 1H), 4.10 (q, 2H, $J=7.2$ Hz), 4.40–4.80 (m, 4H), 7.3 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm): −5.7 (CH_3), 18.0 (C), 25.7 (CH_3), 33.1 (CH_2), 36.2 (CH), 51.7 (CH_3), 62.5 (CH_2), 72.4 (CH_2), 75.4 (CH_2), 78.4 (CH), 127.6–128.3, 137.7 (CH_{Ar}), 171.4 (C_{Ar}); MS (70 eV) *m*/*z* (%): 73 (08), 91 (100).

3.5. General procedure for lactonization

A solution of 20% aqueous HCl (200 μL) was added to a solution of adduct **13** (0.5 g, 1.19 mmol) in MeOH (5 mL). The mixture was stirred at rt for 3 h, then diluted in CH_2Cl_2, washed with saturated $NaHCO_3$ and the organic phase was dried over Na_2SO_4. The solvent was removed in vacuum. The residue was purified by column chromatography on silica gel (Hex./AcOEt 60:40) yielding (4*R*,5*R*)-5-benzyloxy-4-nitromethyltetrahydropyran-2-one **14** as a solid (0.25 g, 85%); $[\alpha]_D^{25}=+52.8$ (*c* 1.02, CH_2Cl_2); ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm): 2.45 (m, 1H), 2.85 (m, 3H), 3.74 (ddd, 1H, $J=7.1$ Hz, $J=6.2$ Hz, $J=4.3$ Hz), 4.26 (dd, 1H, $J=12.0$ Hz, $J=6.2$ Hz), 4.40 (dd, 1H, $J=12.0$ Hz, $J=4.3$ Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm): 31.0 (CH_2), 36.4 (CH), 68.0 (CH_2), 71.5 (CH), 72.0 (CH_2), 76.1 (CH_2), 127.9–128.6 (CH), 136.5 (C), 168.4 (C).

3.5.1. (3*S*,4*S*,5*S*)-5-Hydroxymethyl-3-methyl-4-nitromethyldihydrofuran-2-one, 11a. Mp = 71–72°C; $[\alpha]_D^{25}=+43.6$ (*c* 1.09, MeOH); ^{1}H NMR (200 MHz, CD_3CN) δ (ppm): 1.18 (d, $J=7.6$ Hz, 3H), 2.98 (dq, $J=9.6$, $J=7.6$, 1H), 3.25 (t, $J=5.3$, 1H), 3.48–3.64 (m, 1H), 3.61 (ddd, $J=12.6$, $J=5.3$, $J=3.7$, 1H), 3.78 (ddd, $J=12.6$, $J=5.2$, $J=3.8$), 4.56–4.66 (m, 1H), 4.62 (dd, $J=15.3$, $J=7.2$, 1H), 4.73 (dd, $J=15.3$, $J=7.2$, 1H); ^{13}C NMR (50 MHz, CD_3CN) δ (ppm): 11.1 (CH_3), 37.9 (CH), 38.7 (CH), 60.9 (CH_2), 72.5 (CH_2), 80.3 (CH), 179.3 (C); MS *m*/*z* (%): 158 (M^+-31, 5), 111 (63), 83 (38), 55 (100). Crystallographic data: $C_7H_{11}NO_5$, Mr = 189.17, monoclinic, $P2_1$, $a=6.524(1)$, $b=12.741(2)$, $c=10.437(2)$ Å, $\beta=97.86(2)°$, $V=859.4(3)$ Å^3, $Z=4$, $D_{calcd}=1.46$ g cm^{-3}, $\mu=1.08$ mm^{-1}, $F(000)=400$, $T=291$ K; parallelepiped crystal with dimensions 0.28×0.24×0.10 mm. Lattice parameters refined using 30 reflections in the range $15\leq 2\theta\leq 60°$. Huber four circle diffractometer with a Rigaku rotating anode generator, graphite monochromatized CuKα radiation ($\lambda=1.54178$ Å). 2896 independent reflections with $\sin\theta/\lambda\leq 0.60$ Å^{-1}; $0\leq h\leq 7$, $-15\leq k\leq 15$, $-12\leq l\leq 12$; 2684 with $I\geq 2.0\sigma(I)$. A standard reflection (−2 0 −3) was checked every 50 reflections, no significant decay was observed. The structure was solved by directs methods using SHELXS-86.[8] All H atoms from difference Fourier synthesis. Anisotropic least-squares refinement (SHELXL-93)[9] using F^2; H isotropic with common refined temperature factor ($U=0.049$ Å^2). 302 parameters. $w=1/(\sigma^2(F_o^2)+0.0705P^2+0.06P)$, $R=0.038$, R (all data) = 0.041, $wR=0.098$, $S=1.042$. Final maximum shift to error = 0.001. Maximum and heights in final Fourier synthesis = 0.12 and −0.19 e Å^{-3}. Full lists of atomic coordinates, bond lengths and angles, thermal parameters have been deposited with the Cambridge Crystallographic Data Center (CCDC 186717).

3.5.2. (3*R*,4*S*,5*S*)-5-Hydroxymethyl-3-methyl-4-nitromethyldihydrofuran-2-one, 12a. Oil; $[\alpha]_D^{25}=+113.7$ (*c* 1.16, MeOH); ^{1}H NMR (200 MHz, CD_3CN) δ (ppm): 1.16 (d, 3H, $J=7.0$), 2.65 (dq, 1H, $J=11.7$, $J=7.0$ Hz), 3.10 (ddd, 1H, $J=11.7$ Hz, $J=9.1$ Hz, $J=8.1$ Hz, $J=5.5$ Hz), 3.29 (t, 1H, $J=4.8$ Hz), 3.59 (ddd, 3H, $J=12.8$ Hz, $J=4.8$ Hz, $J=2.2$ Hz), 3.84 (ddd, 1H, $J=12.8$ Hz, $J=4.8$ Hz, $J=3.1$), 4.66 (ddd, 1H, $J=8.1$ Hz, $J=3.1$ Hz, $J=2.2$ Hz), 4.72 (dd, 1H, $J=14.9$ Hz, $J=5.5$ Hz), 4.63 (dd, 1H, $J=14.9$ Hz, $J=9.1$ Hz); ^{13}C NMR (50 MHz, CD_3CN) δ (ppm): 14.7 (CH_3), 38.2 (CH), 43.6 (CH), 61.5 (CH_2), 72.4, 75.0 (CH_2), 79.2 (CH), 179.0 (CH); MS (70 eV) *m*/*z* (%): 158 (6), 111 (70), 83 (46), 55 (100).

3.5.3. (3*S*,4*S*,4*S*)-3-Benzyl-5-hydroxymethyl-4-nitromethyldihydrofuran-2-one, 11b. Mp = 133–134°C; $[\alpha]_D^{25}=+76.5$ (*c* 1.05, MeOH); ^{1}H NMR (200 MHz, CD_3CN) δ (ppm): 2.20–2.60 (l, 1H), 2.81 (dd, $J=15.0$ Hz, $J=8.4$ Hz, 1H), 3.12 (dd, $J=15.0$ Hz, $J=6.6$ Hz, 1H), 3.30–3.41 (m, 1H), 3.41–3.61 (m, 1H), 4.56 (dd, $J=15.5$ Hz, $J=9.1$ Hz, $J=5.3$ Hz, 1H), 4.56–4.64 (m, 1H), 4.73 (dd, $J=15.5$ Hz, $J=8.0$ Hz, 1H), 7.10–7.40 (m, 5H); ^{13}C NMR (50 MHz, CD_3CN) δ (ppm): 32.24 (CH_2), 39.11 (CH), 44.15 (CH), 60.72 (CH_2), 72.05 (CH_2), 80.32 (CH), 127.47 (CH), 129.47 (2CH), 129.54 (2CH), 139.59 (C), 177.43 (C); MS *m*/*z* (%): 265 (1), 91 (100).

3.5.4. (3*R*,4*S*,5*S*)-3-Benzyl-5-hydroxymethyl-4-nitromethyldihydrofuran-2-one, 12b. Mp = 103–104°C; $[\alpha]_D^{25}$ = +45.08 (*c* 1.22, MeOH); ^{1}H NMR (200 MHz, CD_3CN) δ (ppm): 1.80–2.70 (l, 1H), 2.80 (dd, J = 13.4 Hz, J = 8.6 Hz, 1H), 2.96 (ddd, J = 11.0 Hz, J = 8.6 Hz, J = 4.0 Hz, 1H), 3.08–3.28 (m, 1H), 3.28 (dd, J = 13.4 Hz, J = 4.0 Hz, 1H), 3.74 (dd, J = 13.2 Hz, J = 1.4 Hz, 1H), 3.88 (dd, J = 15.0 Hz, J = 3.9 Hz, 1H), 4.05 (dd, 1H, J = 13.2 Hz, J = 2.4 Hz), 4.65 (dd, 1H, J = 15.0 Hz, J = 10.7 Hz), 4.62–4.70 (m, 1H), 7.15–7.45 (m, 5H); ^{13}C NMR (50 MHz, CD_3CN) δ (ppm): 35.99 (CH_2), 40.34 (CH), 43.76 (CH), 61.06 (CH_2), 73.50 (CH_2), 78.82 (CH), 127.32 (CH), 128.78 (2CH), 129.04 (2CH), 136.70 (C), 177.25 (C). Crystallographic data: $C_{13}H_{15}NO_5$, Mr = 265.26, monoclinic, $P2_1$, a = 6.241(2), b = 11.538(4), c = 9.128(2) Å, β = 100.56(3)°, V = 646.2 (3) Å^3, Z = 2, D_{calcd} = 1.36 g cm^{-3}, μ = 0.89 mm^{-1}, $F(000)$ = 280, T = 291 K; parallelepiped crystal with dimensions 0.28×0.24×0.10 mm. Lattice parameters refined using 30 reflections in the range $15 \leq 2\theta \leq 60°$. Huber four circle diffractometer with a Rigaku rotating anode generator, graphite monochromatized CuKα radiation (λ = 1.54178 Å). 2045 independent reflections with $\sin\theta/\lambda \leq 0.60$ Å^{-1}; $0 \leq h \leq 7$, $-13 \leq k \leq 13$, $-10 \leq l \leq 10$ 1978 with $I \geq 2.0\sigma(I)$. A standard reflection (−1 −3 −1) was checked every 50 reflections, no significant decay was observed. The structure was solved by directs methods using SHELXS-86.[8] All H atoms from difference Fourier synthesis. Anisotropic least-squares refinement (SHELXL-93)[9] using F^2; H isotropic with common refined temperature factor (U = 0.075 Å^2). 219 parameters. $w = 1/(\sigma^2(F_o^2)+0.0767P^2+0.05P)$, R = 0.038, R (all data) = 0.039, wR = 0.110, S = 1.09. Final maximum shift to error = 0.001. Maximum and heights in final Fourier synthesis = 0.15 and −0.13 e Å^{-3}. Full lists of atomic coordinates, bond lengths and angles, thermal parameters have been deposited with the Cambridge Crystallographic Data Center (CCDC 186716).

3.6. General procedure to epimerization

DBU (11 μL, 0.08 mmol) was added to a solution of γ-butyrolactone **11a** (0.08 mL, 0.55 mmol), in CH_2Cl_2 (1 mL). The mixture was stirred at rt for 48 h and the solvent was removed in vacuo. The residue was purified by column chromatography on silica gel (Hex./AcOEt 50:50) yielding **12b** (100%).

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