Tetrahedron 71 (2015) 7531–7538

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Diastereoselective and enantioselective preparation of nor-mevaldic acid surrogates through desymmetrisation methodology. Enantioselective synthesis of (+) and (−) nor-mevalonic lactones

José Manuel Botubol-Ares [a], María Jesús Durán-Peña [a], Rosario Hernández-Galán [a], Isidro G. Collado [a], Laurence M. Harwood [b], Antonio J. Macías-Sánchez [a,*]

[a] Departamento de Química Orgánica, Facultad de Ciencias, Campus Universitario Puerto Real, Universidad de Cádiz, Puerto Real, Cádiz 11510, Spain
[b] Department of Chemistry, University of Reading, Whiteknights, Reading RG6 6AD, United Kingdom

ARTICLE INFO

Article history:
Received 21 July 2015
Received in revised form 2 August 2015
Accepted 3 August 2015
Available online 8 August 2015

Dedicated to Professor Steven V. Ley on the occasion of his 70th birthday

Keywords:
Botrytis cinerea
Desymmetrisation
meso-Dialdehyde
Nor-methyl mevaldate

ABSTRACT

Solvent-free desymmetrisation of a *meso*-dialdehyde with chiral alcohols, led to preparation of 4-silyloxy-6-alkyloxytetrahydro-2*H*-pyran-2-one derivatives with a 96% de. This methodology, which yields the corresponding methyl nor-mevaldates with 99% ee, has been applied to the enantioselective synthesis of the (−)-(*R*) and (+)-(*S*) nor-mevalonic acid lactones.

1. Introduction

Enantioselective desymmetrisation of *meso* or prochiral compounds has become a powerful tool in the preparation of enantiomerically pure compounds,[1] using chiral reagents, enzymes[2] or catalysts.[3] Symmetrical or achiral precursors may provide a synthetic advantage by permitting inclusion of a certain degree of complexity before introducing chirality at the desymmetrisation step, instead of incorporating chirality at very early steps of a synthesis.

This approach has been successfully applied to the desymmetrisation of a range of substrates such as dienes,[4] *meso*-anhydrides,[5] *meso*-diols[6] and *meso*-dialdehydes. Desymmetrisation of *meso*-dialdehydes has been performed via Horner–Wadsworth–Emmons reaction,[7] alkylation,[8] carbonyl-ene cyclisation reaction[9] and aldol condensation, either using chiral reagents,[10] an organometallic catalyst[11] or organocatalysis.[12]

In this respect, the synthetic utility of 1,3,5-trioxygenated substrates has led to much interest in their enantiocontrolled preparation.[13] For instance, enantiomerically pure methyl nor-mevaldate **1** has been used as a building block for the synthesis of bioactive molecules such as β-hydroxyacids with antifungal activity,[14] HMG-CoA reductase inhibitors[15] or analogues of statins[16] and 6-alkyl-4-hydroxypyran-2-ones[17] with oestrogenic activity. Furthermore, diverse mevalonic lactone analogues with different substituents in position 4 have been recently synthesised and reported as inhibitors of the mevalonate pathway in the bacterium *Streptococcus pneumoniae*.[18]

As part of our strategy for the design of antifungal agents against *Botrytis* and *Colletotrichum* species,[19] we have recently reported the preparation of 4-hydroxy-6-(1-phenylethoxy)tetrahydro-2*H*-pyran-2-one (**2**) as a selective antifungal agent against the phytopathogen *Botrytis cinerea* via the desymmetrisation reaction of a suitable *meso*-dialdehyde precursor **3** with chiral phenylethanol.[20,21]

In this paper we extend this methodology to the preparation of a range of 6-alkyloxy-4-silyloxytetrahydro-2*H*-pyran-2-ones using different chiral alcohols. The use of the dialdehyde **3** as a building block for the enantioselective preparation of 1,3,5-trioxygenated substrates related to methyl nor-mevaldate **1**, such as nor-mevalonic acid lactones (−)-(*R*)-**4** and (+)-(*S*)-**5** is also described

* Corresponding author. Tel.: +34 956 012704; fax: +34 956 016193; e-mail address: antoniojose.macias@uca.es (A.J. Macías-Sánchez).

http://dx.doi.org/10.1016/j.tet.2015.08.010
0040-4020/

(Fig. 1). These compounds are of interest for structure–activity relationship (SAR) studies.

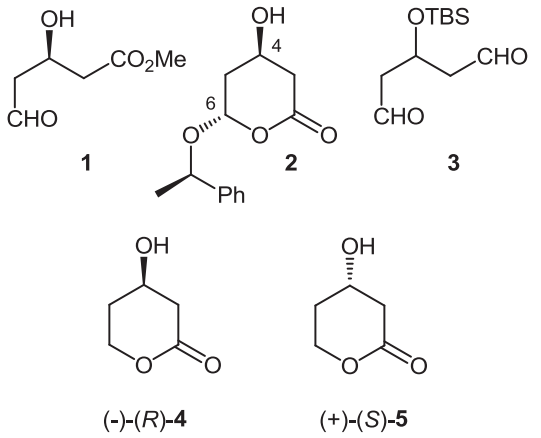
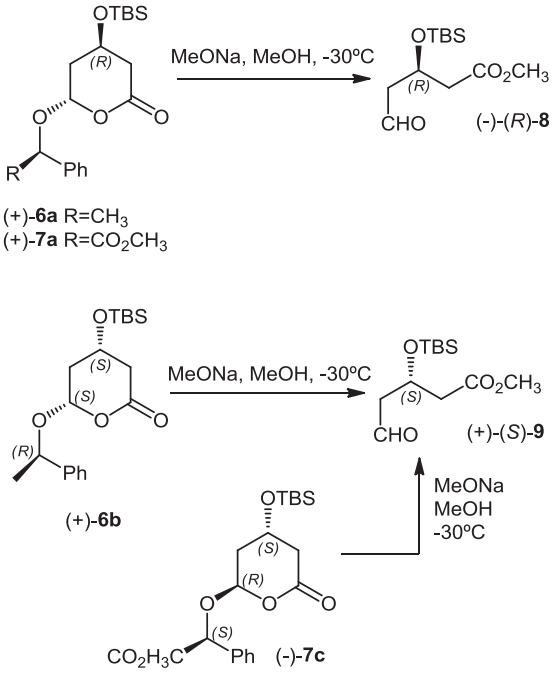


Fig. 1. Structures **1**–**5**.

2. Results and discussion

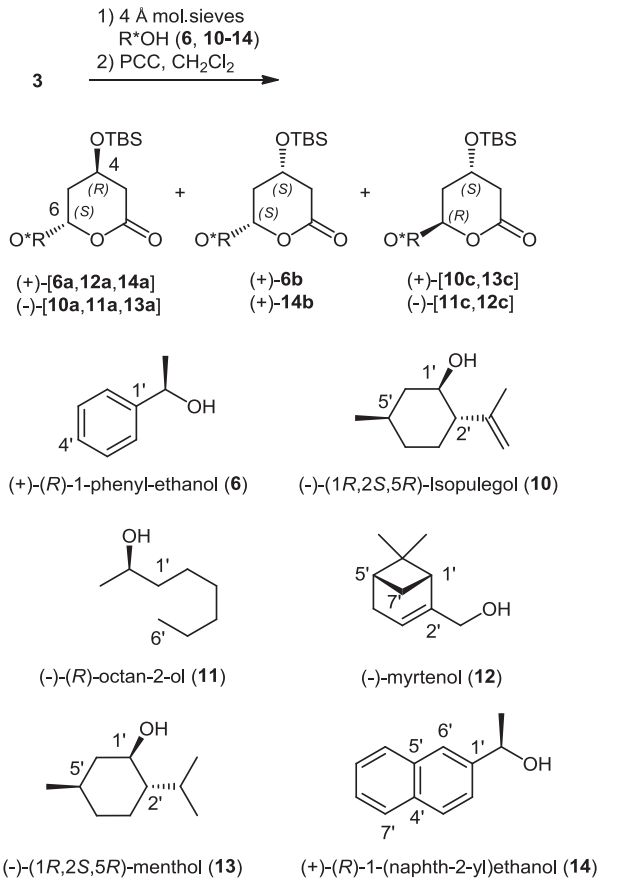
2.1. Optimisation of desymmetrisation reaction

The absolute stereochemistries of chiral 6-arylalkyloxy-4-silyloxytetrahydro-2*H*-pyran-2-ones (+)-**6a** and (+)-**6b** were established unequivocally in previous reports by a combination of X-ray crystallographic analyses of the structurally related tetrahydro-2*H*-pyran-2-ones (+)-**7a** and (−)-**7c**, NOE difference studies and chemical correlation of tetrahydro-2*H*-pyran-2-ones (+)-**6a** and (+)-**7a** with (−)-(*R*) methyl 3-(*tert*-butyldimethylsilyloxy)-5-oxopentanoate (**8**) and of tetrahydro-2*H*-pyran-2-ones (+)-**6b** and (−)-**7c** with (+)-(*S*) methyl 3-(*tert*-butyldimethylsilyloxy)-5-oxopentanoate **9** (Scheme 1).[21]

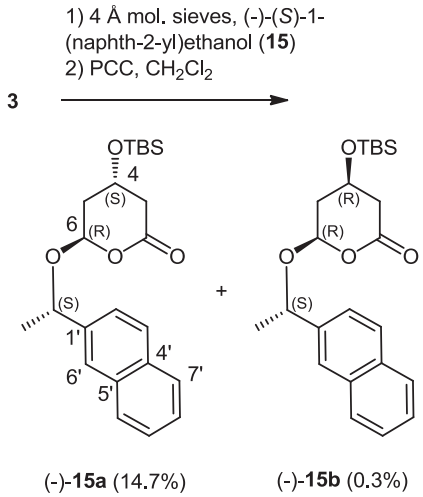


Scheme 1. Chemical correlation of lactones (+)-**6a** and (+)-**7a** with compound (−)-(*R*)-**8** and of lactones (+)-**6b** and (−)-**7c** with (+)-(*S*)-**9**.

Evaluation of the influence of the chiral alcohol structure on the diastereoselectivity of the desymmetrisation process was then undertaken. Consequently, solvent-free conditions,[20] which have been shown to lead to better selectivity than the use of dry THF for the preparation of lactone (+)-**6a**,[21] were applied to a series of commercially available chiral alcohols **10**–**14**, achieving an optimal 14.7% overall yield and 96% de with (+)-(*R*) or (−)-(*S*)-1-(naphthalen-2-yl)ethanol (Schemes 2 and 3, Table 1, entry 6). Best yields and de were obtained when 1-arylethanols were used as chiral auxiliaries (**6** and **14**), suggesting that efficient desymmetrisation required not only a stereogenic centre directly attached to the hydroxyl group, but also a large aromatic group attached to the stereogenic centre, as use of (−)-myrtenol resulted in no asymmetric induction (Table 1, entry 4).



Scheme 2. Solvent-free desymmetrisation of dialdehyde **3** with different chiral alcohols.



Scheme 3. Preparation of (−)-**15a** and (−)-**15b** via solvent-free desymmetrisation of dialdehyde **3** with (−)-(*S*)-1-(naphthalen-2-yl)ethanol.

Table 1
Solvent-free desymmetrisation of dialdehyde **3** with chiral alcohols **6**, **10**–**14**

Entry	R*OH	Products (%)[a]	de (%)
1	(+)-(*R*)-**6**	**6a** (12.3), **6b** (0.6)	92
2	(−)-(1*R*,2*S*,5*R*)-**10**	**10a** (2.5), **10c** (0.4)	72
3	(−)-(*R*)-**11**	**11a** (2.0), **11c** (0.5)	60
4	(−)-**12**	**12a** (2.0), **12c** (2.0)	0
5	(−)-(1*R*,2*S*,5*R*)-**13**	**13a** (2.0), **13c** (0.6)	54
6	(+)-(*R*)-**14**	(+)-**14a** (14.7), (+)-**14b** (0.3)	96

[a] Yields obtained after chromatographic purification.

Stereochemistries of the compounds **10a**–**14a**, **10c**–**13c** and **14b** were established by a combination of NOESY studies, analysis of ^{1}H NMR coupling constants and comparison with related lactones **6a**, **6b**, **7a** and **7c**, whose absolute stereochemistries have been reported before.[21] For example, compound (+)-**14a** presented spectroscopic data closely related to those for compound **6a**, but significantly different to those for compounds **6b** and **7c**, while compound **14b** presented spectroscopic data closely related to those for compound **6b**. Such correlations and the NOE. enhancement observed between H-6 and H-4 for **14b** allowed us to assign their structures as (4*R*,6*S*)-4-((*tert*-butyldimethylsilyl)oxy)-6-((*R*)-1-(naphthalen-2-yl)ethoxy)tetrahydro-2*H*-pyran-2-one (+)-**14a** and (4*S*,6*S*)-4-((*tert*-butyldimethylsilyl)oxy)-6-((*R*)-1-(naphthalen-2-yl)ethoxy)tetrahydro-2*H*-pyran-2-one (+)-**14b**, respectively (^{1}H NMR data for compounds **6a**,**b**, **7a**, **10a**–**14a** and **14b** are presented in Tables 2 and 3; ^{1}H NMR data for compounds **7c** and **10c**–**13c** in Table 4; ^{13}C NMR data for compounds **6a**,**b**, **7a**, **10a**–**14a**, **14b**, **7c** and **10c**–**13c** in Tables S1–S3 of Supplementary data).

Table 2
^{1}H NMR spectroscopic data for **6a**, **6b**, **7a**, **14a** and **14b**[a]

Position	**6a**[20]	**7a**[20]	**14a**	**6b**[20]	**14b**
	δ_H (mult, *J* in Hz)	δ_H (mult, *J* in Hz)	δ_H (mult, *J* in Hz)	δ_H (mult, *J* in Hz)	δ_H (mult, *J* in Hz)
3	α: 2.47 (dd, 5.6, 17.2) β: 2.76 (dd, 4.8, 17.2)	α: 2.50 (dd, 5.6, 17.2) β: 2.85 (ddd, 1.2, 4.8, 17.2)	α: 2.47 (dd, 5.6, 17.4) β: 2.78 (ddd, 0.8, 4.8, 17.4)	α: 2.51 (dd, 9.2, 16.8) β: 2.69 (ddd, 1.8, 5.4, 16.8)	α: 2.51 (dd, 9.2, 17.4) β: 2.69 (ddd, 1.6, 5.6, 17.4)
4	4.33 (m)	4.44 (m)	4.35 (m)	3.98, tt (5.4, 9.2)	3.95 (tt, 5.6, 9.2)
5	α: 1.94 (ddd, 3.6, 5.6, 13.8) β: 1.85 (ddd, 3.6, 6.8, 13.8)	α: 2.13 (dddd, 1.2, 3.8, 4.8, 14.0) β: 1.95 (ddd, 3.8, 6.8, 14.0)	α 1.85 (ddd, 3.6, 7.0, 13.8) β: 1.98 (dddd, 0.8, 4.0, 5.4, 13.8)	α 1.82 (ddd, 7.7, 9.2, 14.0) β: 2.22 (dddd, 1.8, 4.4, 5.4, 14.0)	α: 1.85 (ddd, 7.6, 9.2, 14.0) β: 2.21 (dddd, 1.6, 4.4, 5.6, 14.0)
6	5.25 (dd, 3.6, 5.6)	5.37 (dd, 3.8, 4.8)	5.29 (dd, 3.6, 5.4)	5.04 (dd, 4.4, 7.7)	5.06 (dd, 4.4, 7.6)
Si(*CH*$_3$)(CH$_3$)	0.02[b] (s)	0.04[b] (s)	0.00[b] (s)	0.03[b] (s)	0.01 (s)
Si(CH$_3$)(*CH*$_3$)	−0.03[b] (s)	0.00[b] (s)	−0.07[b] (s)	0.03[b] (s)	0.01 (s)
SiC(*CH*$_3$)$_3$	0.76 (s)	0.79 (s)	0.68 (s)	0.86 (s)	0.85 (s)
2′	7.36–7.28 (m)	7.44–7.36 (m)	7.50–7.42 (m)	7.38–7.28 (m)	7.52–7.44 (m)
3′	7.36–7.28 (m)	7.44–7.36 (m)	7.85–7.81 (m)	7.38–7.28 (m)	7.87–7.78 (m)
4′	7.36–7.28 (m)	7.44–7.36 (m)	—	7.38–7.28 (m)	—
5′	7.36–7.28 (m)	7.44–7.36 (m)	—	7.38–7.28 (m)	—
6′	7.36–7.28 (m)	7.44–7.36 (m)	7.74 (s)	7.38–7.28 (m)	7.74 (s)
7′ and 10′	—	—	7.85–7.81 (m)	—	7.87–7.78 (m)
8′ and 9′	—	—	7.50–7.42 (m)	—	7.52–7.44 (m)
CH$_3$OCO	—	3.69 (s)	—	—	—
ArCH(*CH*$_3$)O	1.46 (d, 6.6)	—	1.55 (d, 6.6)	1.47, d (6.6)	1.56 (d, 6.4)
Ar*CH*O	4.99 (q, 6.6)	5.32 (s)	5.15 (q, 6.6)	5.08, q (6.6)	5.18 (q, 6.4)

[a] Chemical shift values, δ, are in ppm, and the coupling constants, *J*, are in Hz (parentheses).
[b] Interchangeable signals.

Table 3
^{1}H NMR spectroscopic data for **10a**–**13a**[a]

Position	**10a**	**11a**	**12a**	**13a**
	δ_H (mult, *J* in Hz)	δ_H (mult, *J* in Hz)	δ_H (mult, *J* in Hz)	δ_H (mult, *J* in Hz)
3	α: 2.35 (dd, 6.8, 17.2) β: 2.77 (ddd, 0.8, 5.6 17.2)	α: 2.48 (dd, 5.6, 17.4) β: 2.76 (ddd, 0.8, 5.0, 17.4)	α: 2.48 (dd, 5.6, 17.6) β: 2.75 (ddd, 0.8, 4.8, 17.6)	α: 2.47 (dd, 6.0, 17.2) β: 2.76 (ddd, 0.8, 5.2, 17.2)
4	4.30 (m)	4.35 (m)	4.34 (m)	4.36 (m)
5	α: 1.79 (ddd, 4.0, 8.4, 13.6) β: 2.06–1.91 (m)	α: 2.01–1.90 (m) β: 2.01–1.90 (m)	α: 1.99–1.90 (m) β: 1.99–1.90 (m)	α: 1.95–1.85 (m) β: 1.95–1.85 (m)
6	5.50 (t, 4.0)	5.54 (dd, 3.8, 5.0)	5.45 (dd, 4.0, 4.8)	5.62 (t, 4.2)
Si(*CH*$_3$)(CH$_3$)	0.00 (s)	0.07 (s)	0.06 (s)	0.07 (s)
Si(CH$_3$)(*CH*$_3$)	0.00 (s)	0.07 (s)	0.06 (s)	0.07 (s)
SiC(*CH*$_3$)$_3$	0.82 (s)	0.88–0.85 (m)	0.86 (s)	0.89–0.70 (m)
CH(H)O	—	—	4.15 (dd, 1.4, 12.2)	—
CH(H)O	—	—	4.05 (dd, 1.4, 12.2)	—
CH(CH$_3$)O	—	3.92 (sext, 6.4)	—	—
CH(*CH*$_3$)O	—	1.13 (d, 6.4)	—	—
1′	3.68 (dt, 4.2, 10.8)	α: 1.44–1.36 (m) β: 1.54–1.48 (m)	2.14–2.08 (m)	3.64 (dt, 4.4, 10.6)
2′	2.06–1.91 (m)	1.32–1.20 (m)	—	1.24–1.14 (m)
3′	α: 1.48–1.24 (m) β: 1.64–1.54 (m)	1.32–1.20 (m)	5.54 (m)	α: 1.02–0.92 (m) β: 1.68–1.54 (m)
4′	1.48–1.24 (m)	1.32–1.20 (m)	2.27 (m)	α: 0.89–0.70 (m) β: 1.68–1.54 (m)
5′	1.64–1.54 (m)	1.32–1.20 (m)	2.14–2.08 (m)	1.40–1.28 (m)

(*continued on next page*)

Table 3 (*continued*)

Position	**10a**	**11a**	**12a**	**13a**
	δ_H (mult, *J* in Hz)	δ_H (mult, *J* in Hz)	δ_H (mult, *J* in Hz)	δ_H (mult, *J* in Hz)
6′	α: 0.84–0.78 (m) β: 2.06–1.91 (m)	0.88–0.85 (m)	—	α: 0.89–0.70 (m) β: 2.03–1.96 (m)
7′	—	—	α: 1.12 (d, 8.8) β: 2.39 (dt, 5.6, 8.8)	—
C2′C(CH_3)=C(H)(H)	1.60 (s)	—	—	—
C2′C(CH_3)=C(*H*)(H)	4.66 (br s)	—	—	—
C2′C(CH_3)=C(H)(*H*)	4.67 (br s)	—	—	—
C2′*CH*(CH_3)(CH_3)	—	—	—	0.89–0.70 (m)
C2′CH(CH_3)(*CH*$_3$)	—	—	—	0.78 (d, 6.8)
C5′-(*CH*$_3$)(CH_3)	—	—	0.81[b] (s)	—
C5′-(CH_3)(*CH*$_3$)	—	—	1.28[b] (s)	—
C5′-*CH*$_3$	0.89 (d, 6.8)	—	—	0.88 (d, 6.8)

[a] Chemical shift values, δ, are in ppm, and the coupling constants, *J*, are in Hz (parentheses).
[b] Interchangeable signals.

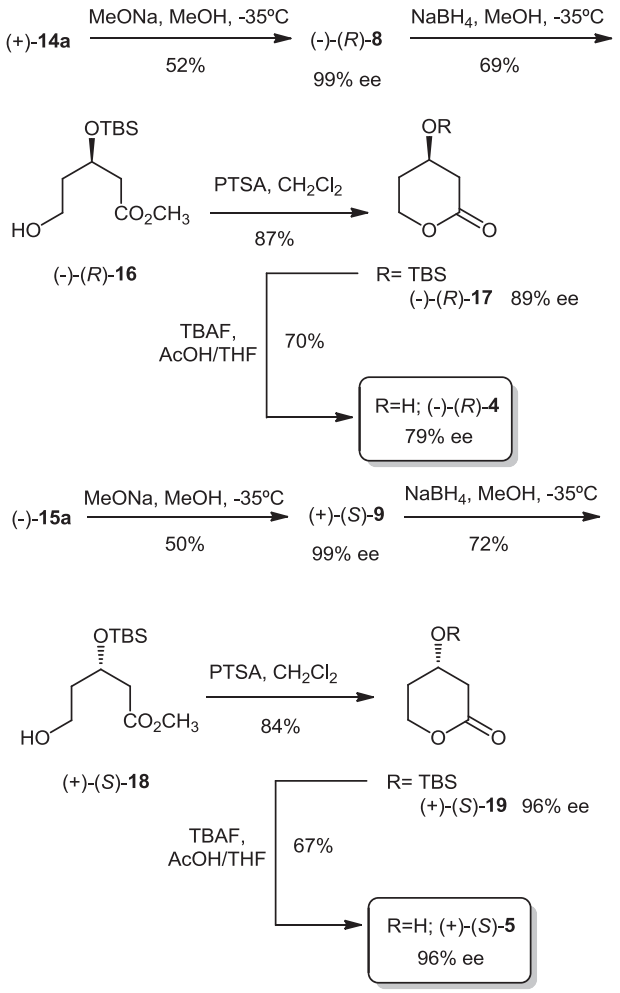
Table 4
^{1}H NMR spectroscopic data for **7c** and **10c**–**13c**[a]

Position	**7c**[20]	**10c**	**11c**	**12c**	**13c**
	δ_H (mult, *J* in Hz)	δ_H (mult, *J* in Hz)	δ_H (mult, *J* in Hz)	δ_H (mult, *J* in Hz)	δ_H (mult, *J* in Hz)
3	α: 2.49 (dd, 4.8, 17.3) β: 2.70 (dd, 4.8, 17.3)	α: 2.45 (dd, 5.2, 17.2) β: 2.69 (dd, 5.2, 17.2)	α: 2.48 (dd, 5.2, 17.2) β: 2.74 (dd, 5.2, 17.2)	α: 2.48 (dd, 5.2, 17.2) β: 2.75 (dd, 5.2, 17.2)	α: 2.48 (dd, 5.0, 17.2) β: 2.73 (dd, 5.0, 17.2)
4	4.36 (quint, 4.8)	4.29 (quint, 5.2)	4.33 (quint, 5.2)	4.34 (quint, 5.2)	4.33 (quint, 5.0)
5	2.16 (t, 4.8)	1.91–1.87 (m)	1.96 (m)	1.98–1.94 (m)	2.04–1.94 (m)
6	5.64 (t, 4.6)	5.42 (dd, 4.2, 5.2)	5.52 (dd, 4.6, 5.2)	5.46 (t, 4.4)	5.50 (t, 5.0)
Si(*CH*$_3$)(CH_3)	0.08[b] (s)	0.05 (s)	0.07 (s)	0.06 (s)	0.07 (s)
Si(CH_3)(*CH*$_3$)	0.07[b] (s)	0.05 (s)	0.07 (s)	0.06 (s)	0.07 (s)
SiC(*CH*$_3$)$_3$	0.87 (s)	0.86 (s)	0.90–0.85 (m)	0.86 (s)	0.91–0.80 (m)
CH(H)O	—	—	—	4.20 (dd, 1.6, 12.8)	—
CH(H)O	—	—	—	4.17 (dd, 1.6, 12.8)	—
CH(CH_3)O	—	—	3.83 (sext, 6.0)	—	—
CH(*CH*$_3$)O	—	—	1.21 (d, 6.4)	—	—
Ar*CH*O	5.47 (s)	—	—	—	—
1′	—	3.60 (dt, 4.4, 10.2)	α: 1.44–1.36 (m) β: 1.54–1.46 (m)	—	3.45 (dt, 4.8, 10.8)
2′	7.44–7.32 (m)	1.96 (ddd, 3.6, 10.2, 12.8)	1.30–1.24 (m)	2.12–2.08 (m)	1.26–1.18 (m)
3′	7.44–7.32 (m)	α: 1.32 (m) β: 1.66–1.57 (m)	1.30–1.24 (m)	5.52 (m)	α: 1.05–0.92 (m) β: 1.65–1.58 (m)
4′	7.44–7.32 (m)	α: 0.88–0.85 (m) β: 1.66–1.57 (m)	1.30–1.24 (m)	2.27 (m)	α: 0.91–0.80 (m) β: 1.65–1.58 (m)
5′	7.44–7.32 (m)	1.50–1.41 (m)	1.30–1.24 (m)	2.12–2.08 (m)	1.42–1.33 (m)
6′	7.44–7.32 (m)	α: 1.02 (m) β: 2.14–2.09 (m)	0.90–0.85 (m)	—	α: 1.05–0.92 (m) β: 2.22–2.16 (m)
7′	—	—	—	α: 1.15 (d, 8.8) β: 2.38 (dt, 5.6, 8.8)	—
C2′C(CH_3)=CH_2	—	1.70 (s)	—	—	—
C2′C(CH_3)=C(*H*)(H)	—	4.76 (br s)	—	—	—
C2′C(CH_3)=C(H)(*H*)	—	4.78 (br s)	—	—	—
C2′CH(CH_3)(*CH*$_3$)	—	—	—	—	0.91–0.80 (m)
C2′CH(*CH*$_3$)(CH_3)	—	—	—	—	0.77 (d, 7.2)
C2′*CH*(CH_3)(CH_3)	—	—	—	—	2.04–1.94 (m)
C5′–(*CH*$_3$)(CH_3)	—	—	—	1.26[b] (s)	—
C5′–(CH_3)(*CH*$_3$)	—	—	—	0.81[b] (s)	—
C5′–*CH*$_3$	—	0.90 (d, 6.4)	—	—	0.91–0.80 (m)
CH$_3$COO	3.70 (s)	—	—	—	—

[a] Chemical shift values, δ, are in ppm, and the coupling constants, *J*, are in Hz (parentheses).
[b] Interchangeable signals.

2.2. Preparation of nor-mevalonic acid lactones (−)-(*R*)-4 and (+)-(*S*)-5

To exemplify the utility of our methodology, and in order to prepare reference compounds for SAR studies,[18] an enantioselective synthesis of nor-mevalonic acid lactones (−)-(*R*)-**4** and (+)-(*S*)-**5**[13e,22] was undertaken from lactones (+)-**14a** and (−)-**15a** (Scheme 4), which were in turn obtained from dialdehyde **3** (Schemes 2 and 3). Treatment of lactone (+)-**14a** with MeONa and MeOH at −35 °C yielded (−)-(*R*)-**8** in 52% yield and 99% ee.[23] Reduction of (−)-(*R*)-**8** with $NaBH_4$ at −35 °C to yield (−)-(*R*)-**16**[24] and subsequent lactonisation with PTSA[25] produced the corresponding lactone (−)-(*R*)-**17** that was subsequently treated with TBAF/AcOH,[26] affording (*R*)-nor-mevalonic acid lactone ((−)-(*R*)-**4**) in 70% yield and 79% ee.[23,27] Desymmetrisation of the dialdehyde **3** with (−)-(*S*)-1-(naphthalen-2-yl)ethanol afforded the corresponding lactone (−)-**15a** in 14.7% overall yield and 96% de (Scheme 3); methanolysis of which, reduction with $NaBH_4$, lactonisation[25] to yield (+)-(*S*)-**19** and deprotection with TBAF/AcOH,[25] yielded (*S*)-nor-mevalonic acid lactone ((+)-(*S*)-**5**) in 67% overall yield and 96% ee.[23]



Scheme 4. Preparation of (*R*) and (*S*) *nor*-mevalonic acid lactones ((−)-(*R*)-**4**) and ((+)-(*S*)-**5**).

3. Conclusions

In summary, the optimization of the desymmetrisation of *meso* dialdehyde **3** led to the selective preparation of (+)-(4*R*,6*S*)-4-((*tert*-butyldimethylsilyl)oxy)-6-((*R*)-1-(naphthalen-2-yl)ethoxy) tetrahydro-2*H*-pyran-2-one (**14a**) and (4*S*,6*R*)-4-((*tert*-butyldimethylsilyl)oxy)-6-((*S*)-1-(naphthalen-2-yl)ethoxy)tetrahydro-2*H*-pyran-2-one-(**15a**) in 96% de when either (*R*)-(+)-1-(naphthalen-2-yl)ethanol or (*S*)-(−)-1-(naphthalen-2-yl)ethanol was used under solvent-free conditions at room temperature. HPLC purification and methanolysis of (+)-(4*R*,6*S*,1′*R*)-(**14a**) or (−)-(4*S*,6*R*,1′*S*)-(**15a**) yielded (−)-(*R*)-methyl 3-(*tert*-butyldimethylsilyloxy)-5-oxopentanoate (−)-(*R*)-(**8**) and (+)-(*S*)-methyl 3-(*tert*-butyldimethylsilyloxy)-5-oxopentanoate (+)-(*S*)-(**9**), respectively, in 99% ee. Further transformation of these substrates allowed the enantioselective preparation of the nor-mevalonic acid lactones (−)-(*R*)-**4** and (+)-(*S*)-**5** (in 42% overall yield and 79% ee and in 41% overall yield and 96% ee, respectively).

4. Experimental section

4.1. General

Unless otherwise noted, materials and reagents were obtained from commercial suppliers and were used without further purification. Dichloromethane was freshly distilled from CaH_2 and tetrahydrofuran was dried over sodium and benzophenone and freshly distilled before use. Air- and moisture-sensitive reactions were performed under an argon atmosphere. Purification by semi-preparative and analytical HPLC was performed, respectively, with 250 mm×10 mm (10 μm particles) and 250 mm×4 mm (5 μm particles) columns using a differential refractometer detector. Silica gel was used for column chromatography. TLC analyses were performed on aluminium plates coated with silica gel with fluorescent indicator (254 nm), 0.25 mm thick. Enantiomeric excesses (ee) were measured by GC using a Cyclosil B chiral column (30 m length×0.25 mm ID, 0.25 μm film thickness), using an FID detector at 320 °C, a split injector (15:1 ratio) at 250 °C, hydrogen as carrier at 10 psi and 1 μL of injection volume. Temperature program is described in the experimental section for every relevant compound. Specific rotations were determined with a digital polarimeter. Infrared spectra were recorded on an FTIR spectrophotometer and peak position reported in wavenumbers (cm^{-1}). ^1H spectra were recorded on spectrometers operating at 300 and 400 MHz. ^{13}C NMR spectra were measured at 75 and 100 MHz with complete proton decoupling. Chemical shifts were referenced to $CDCl_3$ (δ_H 7.25, δ_C 77.0). NMR assignments were made by combination of 1D and 2D techniques. Multiplicities are described using the following abbreviations: s=singlet, d=doublet, t=triplet, q=quartet; quint=quintet; sext=sextet; m=multiplet, br=broad. High-resolution mass spectrometry (HRMS) was recorded with a double-focussing magnetic sector mass spectrometer in positive ion mode, or in a QTOF mass spectrometer in positive ion electrospray mode at 20 V cone voltage.

4.2. Procedures

*4.2.1. General procedure for the preparation of 6-alkyloxy-4-(tert-butyldimethylsilyloxy)tetrahydro-2H-pyran-2-ones (**6a**,**b**, **10a**–**15a**, **14b**, **15b** and **10c**–**13c**): desymmetrisation of 3-(tert-butyldimethylsilyloxy)pentanedial (**3**) under solvent-free conditions followed by PCC oxidation.* The requisite alcohol (see Schemes 2 and 3 of the manuscript) (2.9 mmol) was added to a mixture of 3-(*tert*-butyldimethylsilyloxy)pentanedial (**3**) (1 mmol)[20] and 4 Å molecular sieves (0.5 g for each mmol of **3**) under an argon atmosphere and the mixture stirred for 24 h. The slurry was dissolved in CH_2Cl_2 (20 mL) and added dropwise to a suspension of PCC (3.5 mmol) and powdered molecular sieves 4 Å (twice the weight of the alcohol) in dichloromethane (70 mL) at room temperature. The reaction mixture was stirred vigorously for 18 h, diethyl ether was then added (200 mL) and the mixture was stirred for a further 1 h. The suspension was filtered through a pad of silica gel and washed through with a further quantity of ether (200 mL). The ether was removed under reduced pressure to give the crude mixture of tetrahydro-2*H*-pyran-2-ones, which was purified by column chromatography (petroleum ether/Et_2O, 90:10), to yield the corresponding tetrahydro-2*H*-pyran-2-ones in the ratios and yields shown below and in Table 1 and Schemes 2 and 3 of the manuscript.

*4.2.1.1. (−)-(4R(S),6S(R))-4-((tert-Butyldimethylsilyl)oxy)-6-(((1R,2S,5R)-5-methyl-2-(prop-1-en-2-yl)cyclohexyl)oxy)tetrahydro-2H-pyran-2-one (**10a**).* Yield 9.5 mg, 2.5%. Colourless oil; HPLC t_R=21 min (petroleum ether/ethyl acetate 93:7; flow=3.0 mL/min); $[\alpha]_D^{20}$ −73.7 (*c* 0.1, $CHCl_3$); IR (film) ν_{max} 3073, 2932, 2858, 1749, 1644, 1453, 1378, 1228, 1145, 1024, 889, 837, 781 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) (see Table 3); ^{13}C NMR ($CDCl_3$, 100 MHz) (see Table S2); HRMS (CI^+): *m*/*z* $[M+H]^+$, found 383.2608. $C_{21}H_{39}O_4Si$ requires 383.2618.

*4.2.1.2. (+)-(4S(R),6R(S))-4-((tert-Butyldimethylsilyl)oxy)-6-(((1R,2S,5R)-5-methyl-2-(prop-1-en-2-yl)cyclohexyl)oxy)tetrahydro-2H-pyran-2-one (**10c**).* Yield 1.5 mg, 0.4%. Colourless oil; HPLC t_R=26 min (petroleum ether/ethyl acetate 93:7; flow=3.0 mL/min);

$[\alpha]_D^{20}$ +44.8 (*c* 0.5, $CHCl_3$); IR (film) ν_{max} 3074, 2928, 2858, 1750, 1647, 1458, 1378, 1256, 1153, 1006, 837, 778 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (see Table 4); ^{13}C NMR (100 MHz, $CDCl_3$) (see Table S3); HRMS (CI^+): *m/z* $[M+H]^+$, found 383.2605. $C_{21}H_{39}O_4Si$ requires 383.2618.

*4.2.1.3. (−)-(4R(S),6S(R))-4-((tert-Butyldimethylsilyl)oxy)-6-((R)-octan-2-yloxy)tetrahydro-2H-pyran-2-one (**11a**).* Yield 7.2 mg, 2%. Colourless oil; HPLC t_R=19 min (petroleum ether/ethyl 93:7; flow=3.0 mL/min); $[\alpha]_D^{20}$ −44.9 (*c* 0.1, $CHCl_3$); IR (film) ν_{max} 2930, 2858, 1751, 1464, 1256, 1103, 1008, 837, 778 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (see Table 3); ^{13}C NMR (100 MHz, $CDCl_3$) (see Table S2); HRMS (CI^+): *m/z* $[M+H]^+$, found 359.2625. $C_{19}H_{39}O_4Si$ requires 359.2618.

*4.2.1.4. (−)-(4S(R),6R(S))-4-((tert-butyldimethylsilyl)oxy)-6-((R)-octan-2-yloxy)tetrahydro-2H-pyran-2-one (**11c**).* Yield 1.8 mg, 0.5%. Colourless oil; HPLC t_R=27 min (petroleum ether/ethyl acetate 93:7; flow=3.0 mL/min); $[\alpha]_D^{20}$ −28.3 (*c* 0.2, $CHCl_3$); IR (film) ν_{max} 2932, 2857, 1748, 1469, 1256, 1103, 1021, 838, 778 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (see Table 4); ^{13}C NMR (100 MHz, $CDCl_3$) (see Table S3); HRMS (CI^+): *m/z* $[M+H]^+$, found 359.2625. $C_{19}H_{39}O_4Si$ requires 359.2618.

*4.2.1.5. (+)-(4R(S),6S(R))-4-((tert-Butyldimethylsilyl)oxy)-6-(((1R,5S)-6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl)methoxy)tetrahydro-2H-pyran-2-one (**12a**).* Yield 7.6 mg, 2%. Colourless oil; HPLC t_R=40 min (petroleum ether/ethyl acetate 94:6; flow=0.8 mL/min); $[\alpha]_D^{20}$ +40.0 (*c* 0.2, $CHCl_3$); IR (film) ν_{max} 2929, 2858, 1753, 1472, 1383, 1225, 1102, 1030, 838, 778 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (see Table 3); ^{13}C NMR (100 MHz, $CDCl_3$) (see Table S2); HRMS (CI^+): *m/z* $[M+H]^+$, found 381.2455. $C_{21}H_{37}O_4Si$ requires 381.2461.

*4.2.1.6. (−)-(4S(R),6R(S))-4-((tert-Butyldimethylsilyl)oxy)-6-(((1R,5S)-6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl)methoxy)tetrahydro-2H-pyran-2-one (**12c**).* Yield 7.6 mg, 2%. Colourless oil; HPLC t_R=37 min (petroleum ether/ethyl acetate 94:6; flow=0.8 mL/min); $[\alpha]_D^{20}$ −129.0 (*c* 0.1, $CHCl_3$); IR (film) ν_{max} 2932, 2858, 1752, 1469, 1369, 1256, 1103, 1023, 838, 777 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (see Table 4); ^{13}C NMR (100 MHz, $CDCl_3$) (see Table S3); HRMS (CI^+): *m/z* $[M+H]^+$, found 381.2453. $C_{21}H_{37}O_4Si$ requires 381.2461.

*4.2.1.7. (−)-(4R(S),6S(R))-4-((tert-Butyldimethylsilyl)oxy)-6-(((1R,2S,5R)-2-isopropyl-5-methylcyclohexyl)oxy)tetrahydro-2H-pyran-2-one (**13a**).* Yield 7.7 mg, 2%. Colourless oil; HPLC t_R=16 min (petroleum ether/ethyl acetate 93:7; flow=3.0 mL/min); $[\alpha]_D^{20}$ −67.7 (*c* 0.15, $CHCl_3$); IR (film) ν_{max} 2929, 2858, 1753, 1463, 1369, 1255, 1101, 1023, 838, 777 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (see Table 3); ^{13}C NMR (100 MHz, $CDCl_3$) (see Table S2); HRMS (CI^+): *m/z* $[M+H]^+$, found 385.2764. $C_{21}H_{41}O_4Si$ requires 385.2774.

*4.2.1.8. (+)-(4S(R),6R(S))-4-((tert-Butyldimethylsilyl)oxy)-6-(((1R,2S,5R)-2-isopropyl-5-methylcyclohexyl)oxy)tetrahydro-2H-pyran-2-one (**13c**).* Yield 2.3 mg, 0.6%. Colourless oil; HPLC t_R=21 min (petroleum ether/ethyl acetate 93:7; flow=3.0 mL/min); $[\alpha]_D^{20}$ +21.1 (*c* 0.1, $CHCl_3$); IR (film) ν_{max} 2930, 2859, 1752, 1464, 1369, 1253, 1104, 1013, 837, 778 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (see Table 4); ^{13}C NMR (100 MHz, $CDCl_3$) (see Table S3); HRMS (CI^+): *m/z* $[M+H]^+$, found 385.2766. $C_{21}H_{41}O_4Si$ requires 385.2774.

*4.2.1.9. (+)-(4R,6S)-4-((tert-Butyldimethylsilyl)oxy)-6-((R)-1-(naphthalen-2-yl)ethoxy)tetrahydro-2H-pyran-2-one (**14a**).* Yield 58.8 mg, 14.7%. Colourless oil; HPLC t_R=42 min (petroleum ether/ethyl acetate 93:7; flow=3.0 mL/min); $[\alpha]_D^{20}$ +118.0 (*c* 1.0, $CHCl_3$); IR (film) ν_{max} 3060, 2955, 2858, 1749, 1471, 1382, 1231, 1100, 837, 749 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (see Table 2); ^{13}C NMR (100 MHz, $CDCl_3$) (see Table S1); HRMS (ESI-QTOF): *m/z* $[M+Na]^+$, found 423.1968. $C_{23}H_{32}O_4NaSi$ requires 423.1968; $[M+H-C_6H_{15}SiOH]^+$, found 269.1161. $C_{17}H_{17}O_3$ requires 269.1178.

4.2.1.10. (+)-(4S,6S)-4-((tert-Butyldimethylsilyl)oxy)-6-((R)-1-(naphthalen-2-yl)ethoxy)tetrahydro-2H-pyran-2-one (14b). Yield 1.2 mg, 0.3%. Colourless oil; HPLC t_R=34 min (petroleum ether/ethyl acetate 93:7; flow=3.0 mL/min); $[\alpha]_D^{20}$ +91.4 (*c* 1.4, $CHCl_3$); IR (film) ν_{max} 3056, 2955, 2858, 1749, 1462, 1378, 1255, 1095, 1027, 837, 778 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (see Table 2); ^{13}C NMR (100 MHz, $CDCl_3$) (see Table S1); HRMS (ESI-QTOF): *m/z* $[M+Na]^+$, found 423.1968. $C_{23}H_{32}O_4NaSi$ requires 423.1968; $[M+H-C_6H_{15}SiOH]^+$, found 269.1175. $C_{17}H_{17}O_3$ requires 269.1178.

*4.2.1.11. (−)-(4S,6R)-4-((tert-Butyldimethylsilyl)oxy)-6-((S)-1-(naphthalen-2-yl)ethoxy)tetrahydro-2H-pyran-2-one (**15a**).* Yield 58.7 mg, 14.7%. $[\alpha]_D^{20}$ −118.0 (*c* 1.0, $CHCl_3$).

*4.2.1.12. (−)-(4R,6R)-4-((tert-Butyldimethylsilyl)oxy)-6-((S)-1-(naphthalen-2-yl)ethoxy)tetrahydro-2H-pyran-2-one (**15b**).* Yield 1.3 mg, 0.3%. $[\alpha]_D^{20}$ −91.4 (*c* 1.3, $CHCl_3$).

*4.2.2. Preparation of (−)-(R)-Methyl 3-(tert-butyldimethylsilyloxy)-5-oxopentanoate ((−)-(R)-**8**).* Sodium methoxide (654.5 mg, 12.12 mmol) was added to a solution of tetrahydro-2*H*-pyran-2-one (+)-**14a** (809.0 mg, 2.02 mmol) in dry MeOH (101 mL) at −35 °C. The reaction mixture was stirred at −35 °C for 24 h, then quenched with saturated NH_4Cl (110 mL). The mixture was then allowed to warm to room temperature and diethyl ether (300 mL) was added. The layers were separated and the aqueous phase was further extracted with diethyl ether (3×300 mL). The combined organic layers were washed with brine (2×500 mL), dried over Na_2SO_4 and the solvent was removed under reduced pressure to give a crude reaction product, which was purified by column chromatography (petroleum ether/Et_2O 90:10) to give (*R*)-1-phenylethanol (157.0 mg, 64%) and (−)-(*R*)-**8** (275.0 mg, 52%, 99% ee) as a colourless oil; $[\alpha]_D^{20}$ −10.2 (*c* 0.3, $CHCl_3$); IR (film) ν_{max} 2931, 2898, 2857, 1736, 1438, 1255, 1087, 837, 777 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.75 (1H, t, *J*=2.0 Hz), 4.59 (1H, quint, *J*=6.2 Hz), 3.63 (3H, s), 2.67–2.62 (2H, m), 2.52 (2H, m), 0.80 (9H, s), 0.03 (6H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.8, 171.1, 64.9, 51.6, 50.8, 42.3, 25.5 (3C), 17.8, −4.9 (2C); HRMS (CI^+): *m/z* $[M-CH_3]^+$, found 245.1199. $C_{11}H_{21}O_4Si$ requires 245.1209. The enantiomeric excess of **8** could be determined by chiral gas chromatography, using the general conditions stated above; isocratic 80 °C. t_R (min): 251.36.

*4.2.3. Preparation of (+)-(S)-methyl 3-(tert-butyldimethylsilyloxy)-5-oxopentanoate ((+)-(S)-**9**).* Compound (−)-**15a** (660.0 mg, 1.65 mmol) was converted into (+)-(*S*)-methyl 3-(*tert*-butyldimethylsilyloxy)-5-oxopentanoate ((+)-(*S*)-**9**) (220.0 mg, 50%, 99% ee) following the methodology described above for the synthesis of (−)-(*R*)-**8** from (+)-**14a**. Colourless oil; $[\alpha]_D^{20}$ +10.2 (*c* 0.25, $CHCl_3$). The enantiomeric excess of **9** could be determined by chiral gas chromatography, using the general conditions stated above; isocratic 80 °C. t_R (min): 256.19.

*4.2.4. Preparation of (−)-(R)-methyl 3-(tert-butyldimethylsilyloxy)-5-hydroxypentanoate ((R)-**16**).* Sodium borohydride (28.5 mg, 0.75 mmol) was added to a solution of (*R*)-**8** (153.7 mg, 0.59 mmol) in dry MeOH (101 mL) at −35 °C under an argon atmosphere. The reaction mixture was stirred at −35 °C for 24 h, adding two supplementary portions of $NaBH_4$ (15 mg each portion). Then, 1 M HCl was added until pH 7 (8 mL) and the reaction mixture was allowed to warm to room temperature. Solvent was removed under reduced pressure and ethyl acetate (50 mL) and brine (15 mL) were added. The layers were separated and the aqueous layer was further

extracted with ethyl acetate (3×50 mL). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure to give the crude reaction product, which was purified by column chromatography (petroleum ether/EtOAc 90:10) to give (*R*)-**16** (106.7 mg, 69%) and (*R*)-4-((*tert*-butyldimethylsilyl)oxy)tetrahydro-2*H*-pyran-2-one (*R*)-**17** (12.4 mg, 9%). *Data for (R)-**16***: colourless oil; $[\alpha]_D^{20}$ −2.0 (*c* 3.1, $CHCl_3$); IR (film) ν_{max} 3422, 2930, 1741, 1438, 1257, 1161, 1026, 837, 777 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.30 (1H, ddt, *J*=12.4, 6.4, 4.8 Hz), 3.76–3.66 (2H, m), 3.64 (3H, s), 2.53 (2H, dd, *J*=17.6, 6.4 Hz), 2.47 (2H, dd, *J*=17.6, 6.4 Hz), 2.42 (s, O*H*), 1.85–1.65 (2H, m), 0.84 (9H, s), 0.07 (3H, s), 0.04 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8, 68.0, 59.4, 51.5, 42.1, 38.9, 25.6 (3C), 17.8, −4.8, −4.9; HRMS (CI^+): *m*/*z* $[M-C(CH_3)_3]^+$, found 205.0899. $C_8H_{17}O_4Si$ requires 205.0896.

*4.2.5. Preparation of (+)-(S)-methyl 3-(tert-butyldimethylsilyloxy)-5-hydroxypentanoate ((S)-**18**).* (+)-(*S*)-Methyl 3-(*tert*-butyldimethylsilyloxy)-5-oxopentanoate ((*S*)-**9**) (110.0 mg, 0.42 mmol) was converted into (+)-(*S*)-methyl 3-(*tert*-butyldimethylsilyloxy)-5-hydroxypentanoate ((*S*)-**18**) (85.0 mg, 72%) and (*S*)-**19** (7.0 mg, 7%) following the methodology described above for the synthesis of (*R*)-**16** from (*R*)-**8**. *Data for (S)-**18**:* colourless oil; $[\alpha]_D^{20}$ +2.0 (*c* 0.2, $CHCl_3$).

*4.2.6. Preparation of (−)-(R)-4-((tert-butyldimethylsilyl)oxy)tetrahydro-2H-pyran-2-one ((R)-**17**).* *p*-Toluenesulfonic acid monohydrate (PTSA) (1.8 mg, 0.01 mmol) was added to a solution of (−)-(*R*)-methyl 3-(*tert*-butyldimethylsilyloxy)-5-hydroxypentanoate ((*R*)-**16**) (38.0 mg, 0.15 mmol) in dry CH_2Cl_2 (2.3 mL) at room temperature. When TLC analysis indicated the completion of the reaction (1 h), saturated $NaHCO_3$ was added (3 mL) and the mixture was stirred for a further 15 min. The aqueous phase was then extracted with ethyl acetate (3×25 mL), the combined organic layers were washed with brine (50 mL), dried over Na_2SO_4 and filtered. Evaporation of the solvent gave the crude product that was purified by silica gel column chromatography (petroleum ether/EtOAc 90:10), to yield (*R*)-**17** (28.9 mg, 87%, 89% ee). Colourless oil; $[\alpha]_D^{20}$ −2.8 (*c* 0.1, $CHCl_3$); IR (film) ν_{max} 2930, 2857, 1739, 1472, 1260, 1161, 1085, 837, 778 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.56 (1H, ddd, *J*=11.2, 9.6, 3.9 Hz), 4.30–4.22 (2H, m), 2.69 (1H, dd, *J*=17.4, 5.0 Hz), 2.52 (1H, dd, *J*=17.4, 4.2 Hz), 2.05–1.94 (1H, m), 1.83–1.73 (1H, m), 0.86 (9H, s), 0.06 (3H, s), 0.05 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.0, 65.3, 63.9, 40.0, 31.3, 25.6 (3C), 18.0, −4.8, −4.9; HRMS (CI^+): *m*/*z* $[M-C(CH_3)_3]^+$, found 173.0645. $C_7H_{13}O_3Si$ requires 173.0634. The enantiomeric excess of **17** could be determined by chiral gas chromatography, using the general conditions stated above; isocratic 100 °C. t_R (min): 244.97 (minor), 249.28 (major).

*4.2.7. Preparation of (+)-(S)-4-((tert-butyldimethylsilyl)oxy)tetrahydro-2H-pyran-2-one ((S)-**19**).* (+)-(*S*)-Methyl 3-(*tert*-butyldimethylsilyloxy)-5-hydroxypentanoate ((*S*)-**18**) (48.0 mg, 0.18 mmol) was converted into (+)-(*S*)-4-((*tert*-butyldimethylsilyl)oxy)tetrahydro-2*H*-pyran-2-one ((*S*)-**19**) (35.6 mg, 84%, 96% ee) following the methodology described above for the synthesis of (*R*)-**17** from (*R*)-**16**. Colourless oil; $[\alpha]_D^{20}$ +2.9 (*c* 0.3, $CHCl_3$). The enantiomeric excess of **19** could be determined by chiral gas chromatography, using the general conditions stated above; isocratic 100 °C. t_R (min): 238.88 (major), 242.38 (minor).

*4.2.8. Preparation of (−)-(R)-4-hydroxytetrahydro-2H-pyran-2-one ((R)-**4**).* (−)-(*R*)-4-((*tert*-Butyldimethylsilyl)oxy)tetrahydro-2*H*-pyran-2-one ((*R*)-**17**) (27.4 mg, 0.12 mmol) was converted into (−)-(*R*)-4-hydroxytetrahydro-2*H*-pyran-2-one ((*R*)-**4**) (9.7 mg, 70%, 79% ee) following the methodology described in the literature.[20] Colourless oil; $[\alpha]_D^{20}$ −3.1 (*c* 0.34, $CHCl_3$); IR (film) ν_{max} 3422, 2926, 2875, 1719, 1458, 1383, 1261, 1079 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.57 (1H, ddd, *J*=11.4, 8.0, 4.0 Hz), 4.34 (1H, quint, *J*=5.2 Hz), 4.28 (1H, ddd, *J*=11.4, 6.4, 4.8 Hz), 2.82 (1H, dd, *J*=17.6, 5.2 Hz), 2.58 (1H, ddd, *J*=17.6, 5.2, 1.0 Hz), 2.12 (1H, m), 1.89 (1H, m), 1.64 (s, O*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0, 65.2, 63.4, 39.4, 31.0; HRMS (CI^+): *m*/*z* $[M]^+$, found 116.0475. Calcd for $C_5H_8O_3$ 116.0473. The enantiomeric excess of **4** could be determined by chiral gas chromatography, using the general conditions stated above; isocratic 100 °C. t_R (min): 208.23 (minor), 211.67 (major).

*4.2.9. Preparation of (+)-(S)-4-hydroxytetrahydro-2H-pyran-2-one ((S)-**5**).* (+)-(*S*)-4-((*tert*-Butyldimethylsilyl)oxy)tetrahydro-2*H*-pyran-2-one ((*S*)-**19**) (31.1 mg, 0.14 mmol) was converted into (+)-(*S*)-4-hydroxytetrahydro-2*H*-pyran-2-one ((*S*)-**5**) (10.5 mg, 67%, 96% ee) following the methodology described in the literature.[20] Colourless oil; $[\alpha]_D^{20}$ +3.6 (*c* 0.2, $CHCl_3$). The enantiomeric excess of **5** could be determined by chiral gas chromatography, using the general conditions stated above; isocratic 100 °C. t_R (min): 204.26 (major), 217.71 (minor).

Acknowledgements

This research was supported by grants from MINECO (AGL2012-39798-C02-01) and from the Junta de Andalucía (P07-FQM-02689) (Spain). A.J.M.-S. gratefully acknowledges a Royal Society of Chemistry research fund grant (UK). J.M.B. thanks Junta de Andalucía for Research Fellowship. Use of NMR and mass spectrometry (QTOF) facilities at Servicio Centralizado de Ciencia y Tecnología (SCCYT) of the University of Cádiz is acknowledged.

Supplementary data

^{13}C spectroscopic data for compounds **6a**,**b**, **7a**, **10a**–**14a**, **14b**, **7c** and **10c**–**13c** together with ^1H and ^{13}C NMR spectra for compounds **4**, **6a**,**b**, **7a**, **7c**, **8**, **10a**–**14a**, **10c**–**13c**, **14b**, **16**,**17**, selected NOESY 1D for compounds **11a**, **11c**, **14a** and **14b**, and chiral GC chromatograms for compounds **4**, **5**, **8**, **9**, **17**, and **19**. Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2015.08.010. These data include MOL files and InChiKeys of the most important compounds described in this article.

References and notes

1. (a) Rovis, T. In *New Frontiers in Asymmetric Catalysis*; Mikami, K., Lautens, M., Eds.; Wiley: Hoboken, NJ, 2006; pp 275–311; (b) Anstiss, M.; Holland, J. M.; Nelson, A.; Titchmarsh, J. R. *Synlett* **2003**, 1213; (c) Willis, M. C. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1765; (d) Ward, R. S. *Chem. Soc. Rev.* **1990**, *19*, 1.
2. (a) Garcia-Urdiales, E.; Alfonso, I.; Gotor, V. *Chem. Rev.* **2011**, *111*, PR110; (b) Garcia-Urdiales, E.; Alfonso, I.; Gotor, V. *Chem. Rev.* **2005**, *105*, 313.
3. Hoffmann, R. *Angew. Chem., Int. Ed.* **2003**, *42*, 1096.
4. Nakahara, K.; Fujioka, H. *Symmetry* **2010**, *2*, 437.
5. Atodiresei, I.; Schiffers, I.; Bolm, C. *Chem. Rev.* **2007**, *107*, 5683.
6. Rendler, S.; Oestreich, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 248.
7. (a) Strand, D.; Norrby, P.; Rein, T. *J. Org. Chem.* **2006**, *71*, 1879; (b) Vares, L.; Rein, T. *Org. Lett.* **2000**, *2*, 2611; (c) Tullis, J. S.; Vares, L.; Kann, N.; Norrby, P.; Rein, T. *J. Org. Chem.* **1998**, *63*, 8284; (d) Kann, N.; Rein, T. *J. Org. Chem.* **1993**, *58*, 3802.
8. (a) Bouzbouz, S.; Popkin, M. E.; Cossy, J. *Org. Lett.* **2000**, *2*, 3449; (b) Takemoto, Y.; Baba, Y.; Honda, A.; Nakao, S.; Noguchi, I.; Iwata, C.; Tanaka, T.; Ibuka, T. *Tetrahedron* **1998**, *54*, 15567; (c) Takemoto, Y.; Baba, Y.; Noguchi, I.; Iwata, C. *Tetrahedron Lett.* **1996**, *37*, 3345; (d) Wang, Z.; Deschênes, D. *J. Am. Chem. Soc.* **1992**, *114*, 1090; (e) Roush, W. R.; Park, J. C. *Tetrahedron Lett.* **1990**, *31*, 4707.
9. Grachan, M. L.; Tudge, M. T.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2008**, *47*, 1469.
10. (a) Oppolzer, W.; Walther, E.; Pérez Balado, C.; De Brabander, J. *Tetrahedron Lett.* **1997**, *38*, 809; (b) Oppolzer, W.; De Brabander, J.; Walther, E.; Bernardinelli, G. *Tetrahedron Lett.* **1995**, *36*, 4413; (c) Ziegler, F. E.; Becker, M. R. *J. Org. Chem.* **1990**, *55*, 2800.
11. Dodd, K.; Morton, D.; Worden, S.; Narquizian, R.; Nelson, A. *Chem.—Eur. J.* **2007**, *13*, 5857.
12. Mans, D. M.; Pearson, W. H. *Org. Lett.* **2004**, *6*, 3305.

13. (a) Rosen, T.; Heathcock, C. H. *J. Am. Chem. Soc.* **1985**, *107*, 3731; (b) Theisen, P. D.; Heathcock, C. H. *J. Org. Chem.* **1988**, *53*, 2374; (c) Chauman, K.; Bhatt, R. K.; Falck, J. R.; Capdevila, J. H. *Tetrahedron Lett.* **1994**, *35*, 1825; (d) Kumar, A.; Dittmer, D. C. *J. Org. Chem.* **1994**, *59*, 4760; (e) Loubinoux, B.; Sinnes, J.-L.; O'Sullivan, A. C.; Winkler, T. *Tetrahedron* **1995**, *51*, 3549.
14. (a) Beuerle, T.; Schreier, P.; Brunerie, P.; Bicchi, C.; Schwab, W. *Phytochemistry* **1996**, *43*, 145; (b) Sjögren, J.; Magnusson, J.; Broberg, A.; Schnürer, J.; Kenne, L. *Appl. Environ. Microbiol.* **2003**, *69*, 7554.
15. Carosi, L.; Hall, D. *Can. J. Chem.* **2009**, *87*, 650 and references included therein.
16. Stokker, G. E.; Alberts, A. W.; Anderson, P. S.; Cragoe, E. J.; Deana, A. A.; Gilfillan, J. L.; Hirshfield, J.; Holtz, W. J.; Hoffman, W. F.; Huff, J. W.; Lee, T. J.; Novello, F. C.; Prugh, J. D.; Rooney, C. S.; Smith, R. L.; Willard, A. K. *J. Med. Chem.* **1986**, *29*, 170.
17. Huang, C. -J.; Wang, S. -C.; Kuo, Y. -H.; Hong, Y. -H.; Lin, B. -F.; Hsu, C. U.S. Patent US 20,100,125,102 A1, 2010; *Chem. Abstr.* **2010**, *152*, 561033.
18. Kudoh, T.; Park, C. S.; Lefurgy, S. T.; Sun, M.; Michels, T.; Leyh, T. S.; Silverman, R. *Bioorg. Med. Chem.* **2010**, *18*, 1124.
19. Collado, I. G.; Sanchez, A. J. M.; Hanson, J. R. *Nat. Prod. Rep.* **2007**, *24*, 674.
20. Botubol-Ares, J. M.; Durán-Peña, M. J.; Hernández-Galán, R.; Collado, I. G.; Harwood, L. M.; Macías-Sánchez, A. J. *Bioorg. Med. Chem.* **2015**, *23*, 6325.
21. Buckley, S. L. J.; Drew, M. G. B.; Harwood, L. M.; Macías-Sánchez, A. J. *Tetrahedron Lett.* **2002**, *43*, 3593.
22. (a) Miyashita, M.; Suzuki, T.; Hoshino, M.; Yoshikoshi, A. *Tetrahedron* **1993**, *53*, 12469; (b) Kitanosono, T.; Xu, P.; Kobayashi, S. *Chem. Asian J.* **2014**, *9*, 179.
23. Determined by chiral GC.
24. Novák, L.; Rohály, J.; Poppe, L.; Hornyánszky, G.; Kolonits, P.; Zelei, I.; Fehér, I.; Fekete, J.; Szabó, E.; Záhorszky, U.; Jávor, A.; Szántay, C. *Liebigs Ann. Chem.* **1992**, 145.
25. See, for instance: Yu, X. M.; Han, H.; Blagg, B. S. J. *J. Org. Chem.* **2005**, *70*, 5599.
26. Smith, A. B.; Ott, G. R. *J. Am. Chem. Soc.* **1996**, *118*, 13095.
27. Lower enantiomeric excesses, particularly for (−)-(*R*)-**17** and (−)-(*R*)-**4**, can be attributed to an incomplete removal of PTSA during the work-up.