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TETRAHEDRON: *ASYMMETRY*

Synthesis of 1,1′-methylenedi[(1*R*,1′*R*,3*R*,3′*R*,5*R*,5′*R*)-8-oxabicyclo[3.2.1]oct-6-en-3-ol] and derivatives: precursors of long-chain polyketides

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Abstract

Racemic 1,1′-methylene[(1*RS*,1′*RS*,3*RS*,3′*RS*,5*RS*,5′*RS*)-8-oxabicyclo[3.2.1]oct-6-en-3-ol] ((±)-**6**) derived from 2,2′-methylenedifuran has been resolved kinetically with *Candida cyclindracea* lipase-catalysed transesterification giving 1,1′-methylenedi[(1*R*,1′*R*,3*R*,3′*R*,5*R*,5′*R*)-8-oxabicyclo[3.2.1]oct-6-en-3-ol] (−)-**6** (30% yield, 98% ee) and 1,1′-methylenedi[(1*S*,1′*S*,3*S*,3′*S*,5*S*,5′*S*)-8-oxabicyclo[3.2.1]oct-6-en-3-yl] diacetate (+)-**8**, (40% yield, 98% ee). These compounds have been converted into 1,1′-methylenedi-[(4*S*,4′*S*,6*S*,6′*S*)- and (4*R*,4′*R*,6*R*,6′*R*)-cyclohept-1-en-4,6-diyl] derivatives. © 2001 Published by Elsevier Science Ltd.

1. Introduction

A great variety of natural products of biological interest include polyketides (1,3-polyoxo, 1,3-polyols, aldols).[1] Several approaches for their synthesis have been proposed.[2,3] Inspired by the work of Lautens[4] and Hoffmann et al.[5] who have converted 8-oxabicyclo[3.2.1]oct-6-en-3-one into 7-carbon-1,3-polyols and analogs[6] and by that of Kaku et al.[7] who have transformed cyclohept-3-ene-1,6-diol into 1,3-polyols, we have proposed a new, non-iterative asymmetric synthesis of long-chain 1,3-polyols starting from the now readily available 2,2′-methylenedifuran **1**.[8] The method implies the double [4+3]-cycloaddition of the 1,1,3-trichloro-2-oxyallyl cation to **1**. After reductive work-up a 45:55 mixture of *meso*-**2** and (±)-*threo*-**2** was obtained in 55% yield and separated by fractional crystallization. The *meso* compound was converted into *meso*-**3** that was desymmetrized into diol (−)-**4** (or (+)-**4**) by means of the Sharpless asymmetric dihydroxylation.[9] Further transformations involving combinations of Evans' *anti*[10] and Nasaraka's *syn*[11]

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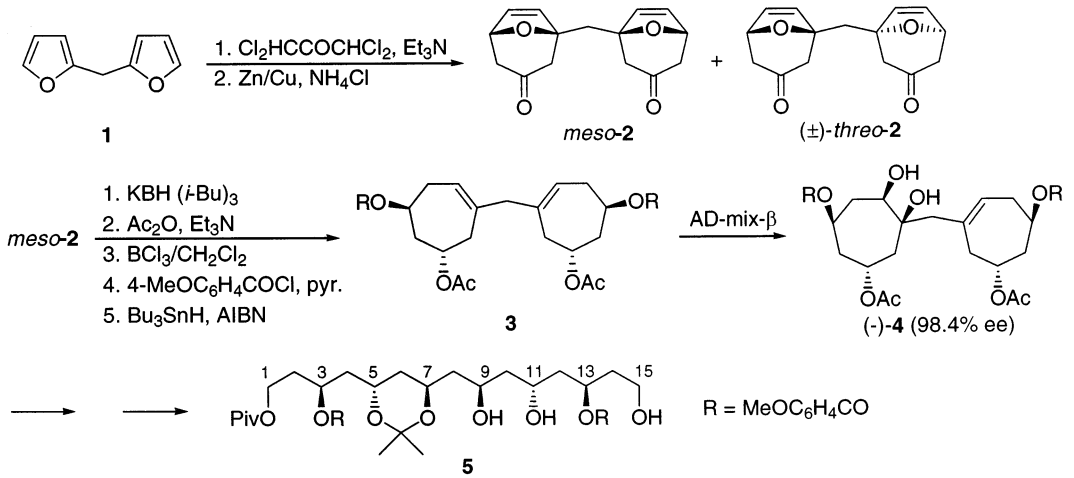
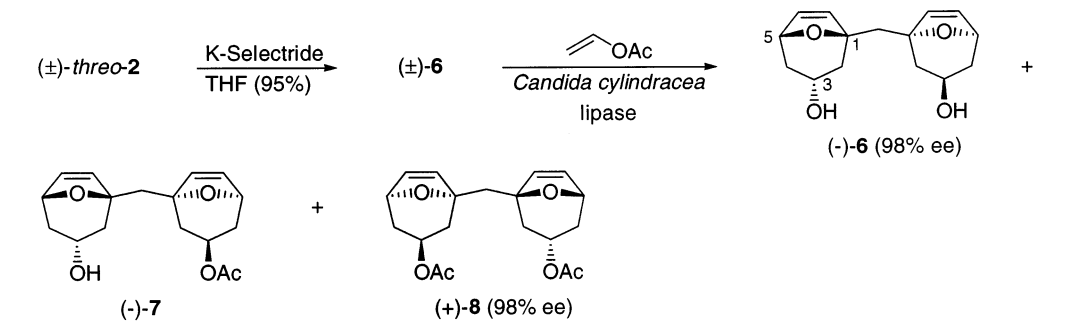
aldol reductions with the Mitsunobu reaction[12] allow, in principle, 16 diastereomeric pentadeca-1,3,5,7,9,11,13,15-octols (e.g. **5**) and analogs (Scheme 1) to be prepared. If the *syn* relationship between the 4-methoxybenzoates at C-3 and C-13 (atom numbering of **5**) could be changed into an *anti* relative configuration, all possible stereomeric pentadeca-1,3,5,7,9,11,13,15-octols could be produced in both enantiomeric forms. In fact, this could be achieved by applying to *threo*-**2** the chemistry developed for *meso*-**2**. To be useful, that plan requires obtaining enantiomerically pure (+)-**2** and (−)-**2** or of more advanced *threo* synthetic intermediates in the conversion to pentadecaoctols. Herein, we disclose a solution to this problem which uses a lipase-catalysed transesterification for the kinetic resolution of *threo*-diol (±)-**6** obtained by double reduction of (±)-*threo*-**2** with K-Selectride in THF (Scheme 2).



Scheme 1.



Scheme 2.

2. Results and discussion

Several commercially available lipases (from *Ps. cepacia* (40 U/mg), *Fluorescens* (36 U/mg), pig pancreas (20 U/mg), *Aspergillus niger* (0.81 U/mg), *Candida antartica* (3.1 U/mg) and *Mucor*

miehei (1.6 U/mg) were tested for their ability to catalyse the transesterification of (±)-**6** with vinyl acetate using THF and $CHCl_3$ as solvents.[13] None were effective. Finally, we found that lipase from *Candida cylindracea* (CCL) (2.4 U/mg) was able to catalyse the desired transesterification, the rate and enantioselectivity depending on the solvent[14] (Table 1).

Table 1
Candida cylindracea lipase (CCL)-catalysed acylation of (±)-*threo*-**6**[a]

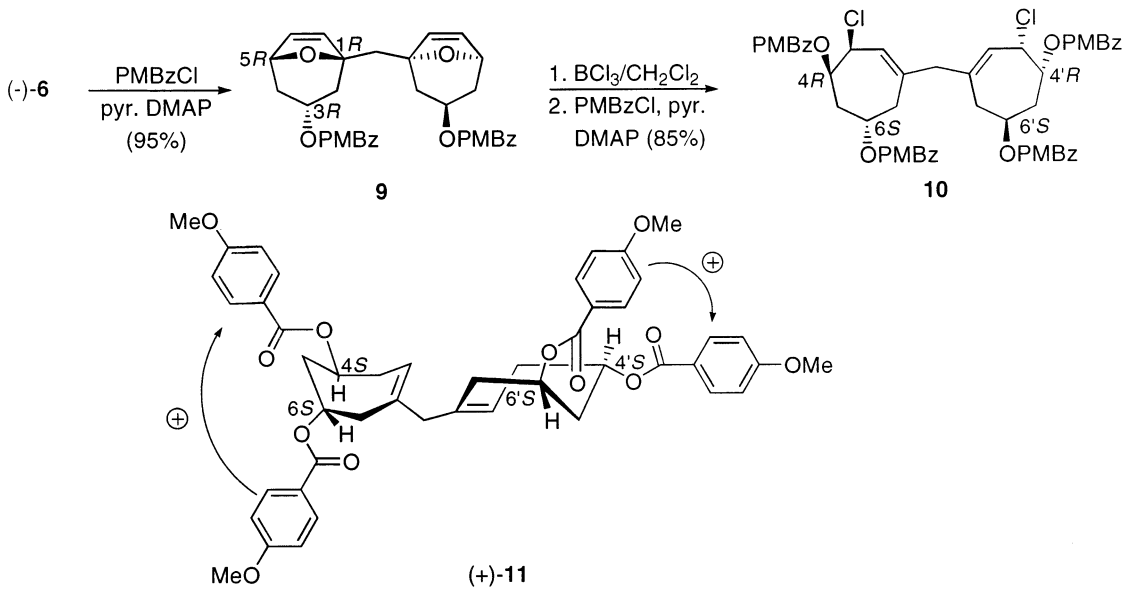
Entry	Product:	(−)-**6**		(−)-**7**		(+)-**8**	
	Solvent	Ee (%)[b]	Yield (%)[c]	Ee (%)[d]	Yield (%)[c]	Ee (%)[e]	Yield (%)[c]
1	$CHCl_3$	30	65	80	15	–	–
2	THF	20	60	60	20	–	–
3	Toluene	50	30	75	15	90	30
4	Cyclohexane	70	30	40	15	90	30
5	Toluene/THF (1:1)	60	35	80	20	80	20
6	Cyclohexane/THF (1:1)	70	35	40	15	90	35
7	Vinyl acetate	98	30	80	10	98	40
8	Vinyl acetate[f]	85	20	80	20	85	40
9	Vinyl acetate[g]	70	35	80	15	70	35
10	Vinyl acetate[h]	80	20	80	15	80	40

[a] Unless otherwise stated, all assays were carried out with 4800 U/mmol of Fluka CCL (2.4 U/mg) in 0.1 M solutions of the substrate in anhydrous solvents at 25 mg scale and in the presence of 2.7 mol equiv. of vinyl acetate for 24 h.
[b] Determined by ^{19}F NMR (376.5 MHz) of Mosher's diester.
[c] Isolated product after column chromatography.
[d] Determined by ^{19}F NMR (376.5 MHz) of Mosher's ester.
[e] Determined by ^{19}F NMR (376.5 MHz) of Mosher's diester of diol (+)-**6** resulting from the saponification of (+)-**8**.
[f] Reaction time: 96 h.
[g] 2400 U/mmol CCL.
[h] 9600 U/mmol CCL.

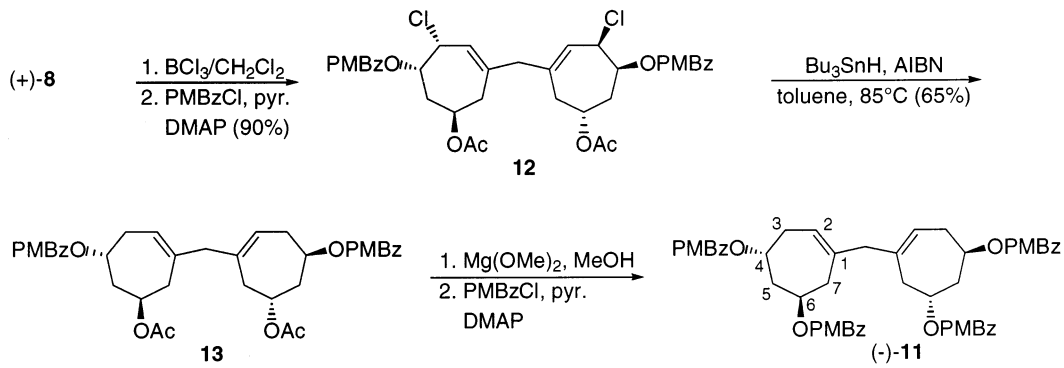
In all cases alcohol (+)-**6** with (1*S*,1′*S*,3*S*,3′*S*,5*S*,5′*S*)-configuration (vide infra) reacted faster giving diacetate (+)-**8** and diol (−)-**6**, together with a small amount of the monoacetate (−)-**7**. The extent and the enantioselectivity of the acylation of (±)-**6** depends on the nature of the solvent. As shown in Table 1 (entry 7) the best results were obtained when the transesterification reaction was carried out using vinyl acetate as reagent and solvent. No significant improvement of either yield or enantioselectivity was obtained in this solvent by increasing the reaction time (entry 8) or by increasing or decreasing the amount of enzyme (entries 9 and 10). Diacetate (+)-**8** was converted quantitatively into diol (+)-**6** on treatment with an excess of K_2CO_3 in MeOH solution (98% ee, Mosher's diester). Monoacetate (−)-**7** was methanolyzed (K_2CO_3/MeOH) into diol (−)-**6** (80% ee, Mosher's diester).

The absolute configurations of diol (−)-**6** and diacetate (+)-**8** were determined by circular dichroism (CD) of the tetrakis(paramethoxybenzoates) (+)-**11** and (−)-**11** derived from (−)-**6** and (+)-**6**, respectively, by means of transformations that do not involve the stereogenic centers of the diols (−)-**6** and (+)-**6** and of the following intermediates (Scheme 3). Thus, diol (−)-**6** was

esterified first with paramethoxybenzoyl chloride in pyridine (with a catalytic amount of 4-dimethylaminopyridine (DMAP)) giving **9** in 95% yield. Treatment of **9** with BCl_3 in CH_2Cl_2[8] afforded a dichlorodiol that was esterified with paramethoxybenzoyl chloride (pyridine, DMAP) giving **10** in 85% yield. Reductive dechlorination of **10** with Bu_3SnH (toluene, 2,2′-azobisisobutyronitrile (AIBN), 86°C) provided (+)-**11** in 70% yield (Scheme 3). Similarly, diol (+)-**6** was converted into (−)-**11**. Alternatively, the diacetate (+)-**8** was treated with BCl_3 to give a dichlorodiol that was esterified into **12** (90% yield, two steps). Reductive dechlorination of **12** (Bu_3SnH, AIBN, toluene, 85°C) provided tetraester **13** in 65% yield. Selective deacylation with $Mg(OMe)_2$ in methanol[8] followed by esterification with paramethoxybenzoyl chloride (pyridine, DMAP) provided the tetrakis(paramethoxybenzoate) (−)-**11** in 90% yield (Scheme 4).



Scheme 3.



Scheme 4.

Molecular models suggest that the C_2-symmetric tetrakis(paramethoxybenzoates) (+)-**11** and (−)-**11** maintain pairs of aromatic chromophores with positive (see Scheme 3) and negative, respectively, intrinsic chirality for the *trans*-cyclohept-1-en-4,6-diyl bis(paramethoxybenzoate)

moieties. Molecular dynamic simulation[15] was carried out for (−)-**11** (with the (4*R*,4′*R*,6*R*,6′*R*)-configuration) over 100 ps at 1000 K, after heating from 0 K for 5 ps. Constant temperature was maintained throughout the simulation by coupling to an external bath with a relaxation constant of 0.5 ps. Conformers were sampled each ps and were independently minimized by the MMX force field using the Polak–Ribiere conjugate gradient to 0.1 kcal/mol convergence. The first 50 ps were considered as equilibration time and were discarded. This simulation led to a negative improper torsion angle for the O-C(6)/C(4)-O moiety of (−)-**11** varying between −60 and −25°, never becoming positive. Thus, exciton coupling between the pairs of paramethoxybenzoate chromophores[16] of (−)-**11** must lead to a negative couplet (double Cotton Effect) in its CD spectrum, as observed for (−)-**11** (Fig. 1). Similarly a positive couplet is expected for the CD spectrum of (+)-**11**, as observed ($\Delta\varepsilon_{262}=+1.0$; $\Delta\varepsilon_{244}=-0.1$). The inflexion points of the couplets observed for (+)-**11** and (−)-**11** at ca. 250 nm coincide with the wavelength of maximum absorbance in the UV absorption spectra of these compounds ($\lambda_{max}=252$ nm, $\varepsilon=20\,000$). Because of an exciton coupling between the alkene and paramethoxybenzoate chromophores,[8] the Cotton effects at lower wavelength (244 nm, Fig. 1) are smaller than those at the higher wavelength (262 nm). These data establish the (4*S*,4′*S*,6*S*,6′*S*)- and the (4*R*,4′*R*,6*R*,6′*R*)-configuration of (+)-**11** and (−)-**11**, respectively, and thus the (1*R*,1′*R*,3*R*,3′*R*,5*R*,5′*R*)- and (1*S*,1′*S*,3*S*,3′*S*,5*S*,5′*S*)-configuration of diol (−)-**6** and (+)-**6**, respectively.

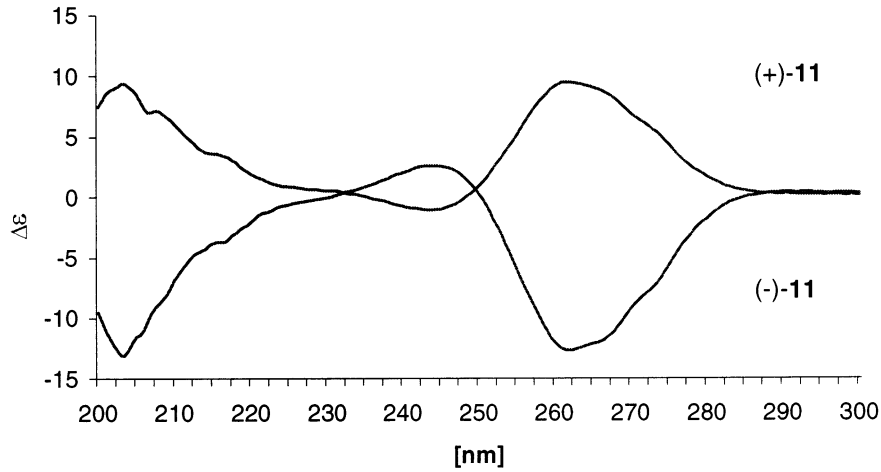


Figure 1. CD spectra of C_2-symmetric (+)-**11** and (−)-**11** in CH_3CN

3. Conclusion

The *threo*-1,1′-methylenedi[(1*RS*,1′*RS*,5*SR*,5′*SR*)-8-oxabicyclo[3.2.1]oct-6-en-3-one] ((±)-**2**) obtained in 30% yield together with *meso*-**2** is not a racemic waste anymore. The racemic 1,1′-methylenedi[(1*RS*,1′*RS*,3*RS*,3′*RS*,5*RS*,5′*RS*)-8-oxabicyclo[3.2.1]oct-6-en-3-ol] ((±)-**6**) obtained by reduction of (±)-**2** has been converted into (−)-**6** (1*R*,1′*R*,3*R*,3′*R*,5*R*,5′*R*) and 1,1′-methylenedi[(1*S*,1′*S*,3*S*,3′*S*,5*S*,5′*S*)-8-oxabicyclo[3.2.1]oct-6-en-3-yl] diacetate ((+)-**8**) in 98% ee with 30 and 40% yield, respectively.[17] Diacetate (+)-**8** can be saponified into (+)-**6**. Compounds (−)-**6** and (+)-**8** have been converted into 1,1′-methylenedi[(4*S*,4′*S*,6*S*,6′*S*)- and (4*R*,4′*R*,6*R*,6′*R*)-cyclohept-1-en-4,6-diyl] derivatives, respectively, potential precursors in the synthesis of long-chain 1,3-polyols.[8]

4. Experimental

4.1. General, see Ref. 18

Circular dichroism spectra were recorded on a JOBIN YVON MARK VI using cubic quartz cell (length 0.1 cm) and calibrated with D-(+)-10-camphorsulfonic acid. Enzymes were purchased from Fluka (Fluka Chemie AG, CH-9471 Buchs, Switzerland) and used as delivered. All assays were carried out with 4800 U/mmol of enzyme in 0.1 M solutions of the substrate and in the presence of at least 2.7 mol. equiv. of vinyl acetate.

4.2. Kinetic resolution of (±)-threo-**6**

Lipase from *Candida cylindracea* (CCL, 2.4 U/mg, 14400 U, 6.0 g) was added to a suspension of (±)-*threo*-**2** (800 mg, 3.0 mmol, obtained by reduction of (±)-**2** with K-Selectride[8] in 90% yield) in vinyl acetate (30 mL) under vigorous stirring at 25°C. After stirring (250 rpm) at 25°C for 24 h the mixture was filtered (Celite), rinsing with CH_2Cl_2. Solvent evaporation and flash chromatography on silica gel with 96:4 CH_2Cl_2/MeOH afforded first 420 mg (40%) of (+)-**8**, then 120 mg (13%) of **7** and finally 240 mg (30%) of (−)-**6**.

4.2.1. Data for (−)-1,1′-methylenedi[(1R,1′R,3R,3′R,5R,5′R)-8-oxabicyclo[3.2.1]oct-6-en-3-ol] (−)-**6**

White solid (98% ee); mp 145–146°C (CH_2Cl_2/AcOEt, 1:1). $[\alpha]_{589}^{25}=-110$, $[\alpha]_{577}^{25}=-114$, $[\alpha]_{546}^{25}=-122$, $[\alpha]_{435}^{25}=-207$, $[\alpha]_{403}^{25}=-263$ ($c=1.0$, $CHCl_3$). IR ($CHCl_3$): 3422, 2940 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): 6.41 (dd, 2H, $^3J=5.9$ Hz), 6.28 (dd, 2H, $^3J=5.9$, 1.5 Hz), 4.75 (d, 2H, $^3J=3.5$ Hz), 3.99 (br. s, 2H), 2.29 (br. s, 2H), 2.17 (ddd, 2H, $^2J=14.7$ Hz, $^3J=5.7$, 4.0 Hz), 2.03 (dd, 2H, $^2J=14.7$ Hz, $^3J=16.2$ Hz), 2.30 (s, 2H). ^{13}C NMR ($CDCl_3$, 100.6 MHz): 138.2, 134.0, 84.2, 78.1, 65.7, 44.3, 42.6, 35.5. MS (CI/NH_3): m/z 282 (4, $[M+NH_4^+]$), 265 (100, $[M+H]^+$), 247 (73), 229 (23). Anal. calcd for $C_{15}H_{16}O_4$: C, 69.22; H, 6.20. Found: C, 69.34; H, 6.32.

4.2.2. Data for (−)-1-{[(1R,3R,5R)-3-hydroxy-8-oxabicyclo[3.2.1]oct-6-enyl]methyl}-[(1R,3R,5R)-8-oxabicyclo[3.2.1]oct-6-en-3-yl] acetate (−)-**7**

Colorless oil (80% ee). $[\alpha]_{589}^{25}=-4.9$, $[\alpha]_{577}^{25}=-5.2$, $[\alpha]_{546}^{25}=-6.5$, $[\alpha]_{435}^{25}=-13$, $[\alpha]_{403}^{25}=-16$ ($c=1.0$, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz): 6.39 (d, 1H, $^3J=5.9$ Hz), 6.28 (dd, 1H, $^3J=5.9$, 1.5 Hz), 6.15 (d, 1H, $^3J=5.9$ Hz), 6.05 (dd, 1H, $^3J=5.9$, 1.5 Hz), 5.03 (dd, 1H, $^3J=6.0$, 5.9 Hz), 4.75 (br. d, 1H, $^3J=3.5$ Hz), 4.68 (br. d, 1H, $^3J=3.5$ Hz), 3.98 (dd, 1H, $^3J=6.0$, 5.9 Hz), 2.32 (br. s, 1H), 2.15 (m, 2H), 2.11 (m, 1H), 2.05–1.98 (m, 3H), 1.98 (s, 3H), 1.85 (d, 1H, $^2J=16.2$ Hz), 1.71 (d, 1H, $^2J=16.2$ Hz), 1.64 (d, 1H, $^2J=16.2$ Hz), 1.52 (d, 1H, $^2J=16.2$ Hz). ^{13}C NMR ($CDCl_3$, 100.6 MHz): 170.2, 137.9, 135.8, 134.0, 131.9, 84.1, 83.6, 77.8, 77.7, 67.2, 65.5, 44.3, 44.1, 38.4, 35.4, 31.6, 21.4. MS (CI/NH_3): m/z 324 (7, $[M+NH_4^+]$), 307 (100, [M+1]), 289 (5), 247 (30), 229 (15). Anal. calcd for $C_{17}H_{22}O_5$: C, 66.65; H, 7.23. Found: C, 66.82; H, 7.44.

4.2.3. Data for (+)-1,1′-methylenedi[(1S,1′S,3S,3′S,5S,5′S)-8-oxabicyclo[3.2.1]oct-6-en-3-yl] diacetate (+)-**8**

White solid (98% ee); mp 124–125°C (Et_2O/petroleum ether, 3:1). $[\alpha]_{589}^{25}=+83$, $[\alpha]_{577}^{25}=+91$, $[\alpha]_{546}^{25}=+103$, $[\alpha]_{435}^{25}=+186$, $[\alpha]_{403}^{25}=+231$ ($c=1.0$, $CHCl_3$). IR ($CHCl_3$): 3430, 3080, 1725, 1420 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): 6.15 (d, 2H, $^3J=5.9$ Hz), 6.05 (dd, 2H, $^3J=5.9$, 1.5 Hz),

5.03 (dd, 2H, $^3J=6.0$, 5.9 Hz), 4.68 (br. d, 2H, $^3J=3.5$ Hz), 2.16 (ddd, 2H, $^2J=15.0$ Hz, $^3J=6.0$, 4.1 Hz), 2.06 (dd, 2H, $^2J=15.0$ Hz, $^3J=6.0$ Hz), 1.99 (s, 2H), 1.95 (s, 6H), 1.75 (d, 2H, $^2J=16.2$ Hz), 1.55 (d, 2H, $^2J=16.2$ Hz). ^{13}C NMR ($CDCl_3$, 100.6 MHz): 170.3, 135.9, 132.1, 83.8, 77.7, 67.3, 44.3, 38.5, 31.1, 21.5. MS (CI/NH_3): m/z 366 (20, [M+NH_4^+]), 349 (100, [M+1]), 331 (7), 289 (40), 229 (34). Anal. calcd for $C_{19}H_{24}O_6$: C, 65.50; H, 6.94. Found: C, 65.72; H, 7.03.

4.3. Methanolysis of acetates (–)-7 and (+)-8

Anhydrous K_2CO_3 (10 equiv.) was added to a solution of (–)-**7** or (+)-**8** (0.03 mmol) in MeOH (1 mL) and the mixture was stirred for 12 h at 20°C. After filtration through a Celite pad, addition of NH_4Cl (50 mg) and filtration through another Celite pad, the solution was evaporated to afford a colorless oil which solidified on standing.

4.3.1. Data of (+)-6

White solid (100%). $[\alpha]_{589}^{25}=+108$ ($c=1.0$, $CHCl_3$).

4.3.2. Correlation of (–)-7 with (–)-6

The above procedure was followed starting from (–)-**7** (80% ee). White solid (100%). $[\alpha]_{589}^{25}=-82$ ($c=1.0$, $CHCl_3$).

4.4. Synthesis of Mosher's esters. General procedure

(+)-(*S*)-α-Methoxy-α-trifluormethylphenylacetyl chloride (1.25 equiv.), Et_3N (1.25 equiv.) and DMAP (0.015 equiv.) were added to a solution of **6** or **7** (0.02 mmol) in anhydrous CH_2Cl_2 (1 mL), and the solution was stirred for 12 h at 20°C. After washing with saturated $NaHCO_3$ (1 mL, twice) and 5% HCl (1 mL, twice), the organic phase was dried ($MgSO_4$) and evaporated to afford a pale yellow oil.

4.4.1. Data for Mosher's diester of (–)-6

^{19}F NMR (376.5 MHz): –75.30 ppm.

4.4.2. Data for Mosher's diester of (+)-6

^{19}F NMR (376.5 MHz): –75.23 ppm.

4.4.3. Data for Mosher's ester of (–)-7

^{19}F NMR (376.5 MHz): –75.26 ppm.

4.4.4. Data for Mosher's ester of (+)-7

^{19}F NMR (376.5 MHz): –75.35 ppm.

4.5. Diol protection as paramethoxybenzoates. General procedure

To a solution of the corresponding diol (0.1 mmol) in pyridine (0.5 mL) were added *p*-methoxybenzoyl chloride (68.3 mg, 0.4 mmol) and DMAP (2 mg) and the mixture was stirred at 20°C for 24 h. Dry MeOH (0.25 mL) was added and the solution was stirred for an additional hour at 20°C. The solvent was evaporated under reduced pressure. The residue was taken up in

CH_2Cl_2 (5 mL) and washed with 3% aqueous HCl (5 mL), then with a saturated aqueous solution of $NaHCO_3$ (5 mL, twice). Drying ($MgSO_4$), solvent evaporation and flash chromatography on silica gel with a 50:50 mixture of petroleum ether/Et_2O afforded the corresponding PMBz-derivatives.

4.6. Ring opening reactions of compounds (+)-**8** and **9**

To a stirred solution of (+)-**8** or **9** (0.36 mmol) in CH_2Cl_2 (10 mL) at −10°C a 0.1 M solution of BCl_3 in CH_2Cl_2 (1.1 mL, 0.11 mmol) was slowly added. After stirring at −10°C for 4 h, the solution was gently allowed to reach 20°C, and a saturated aqueous solution of $NaHCO_3$ (10 mL) precooled to 0°C was added under vigourous stirring. The aqueous layer was extracted with CH_2Cl_2 (10 mL, three times). The combined phases were dried ($MgSO_4$) and the solvent was evaporated under reduced pressure. The resulting oil was taken up in dry pyridine (2 mL) and reacted with *p*-methoxybenzoyl chloride (246 mg, 1.44 mmol), as indicated in the general procedure to afford **12** (90%) and **10** (80%), respectively.

4.7. Hydrodehalogenation of compounds **10** and **12**

A mixture of **10** or **12** (0.25 mmol), toluene (1.0 mL), Bu_3SnH (245 mg, 0.84 mmol) and AIBN (3.5 mg, 0.021 mmol) was stirred at 85°C for 4 h. The solvent was evaporated and the residue taken up in MeCN (1.5 mL). After extraction with pentane (0.5 mL, five times) and solvent evaporation, the residue was taken up in Et_2O (1.5 mL). KF (1.0 mg) was added and the mixture stirred for 4 h at 20°C. Filtration and solvent evaporation under reduced pressure afforded a residue which was dissolved in CH_2Cl_2 (1.5 mL) and successively washed with 3% aqueous HCl (0.5 mL, twice) and saturated $NaHCO_3$ (0.5 mL, twice). The organic phase was dried ($MgSO_4$). Solvent evaporation, flash chromatography on silica gel with a 70:30 mixture of Et_2O/petroleum ether afforded (+)-**11** (70%) and **13** (65%), respectively.

4.8. Selective deacylation and PMBz-protection of **13**

To a solution of **13** (80 mg, 0.13 mmol) in anhydrous MeOH (5 mL) was added a 0.7 M solution of $Mg(OMe)_2$ in MeOH (1.5 mL, 2.14 mmol) and the mixture was stirred at 20°C under Ar for 4 h. After acidification with 2.5 M oxalic acid in anhydrous MeOH and stirring for 1 h, the solution was filtered (Celite). Solvent evaporation and flash chromatography on silica gel with a 95:5 mixture of CH_2Cl_2/MeOH afforded a colorless oil which was esterified with *p*-methoxybenzoyl chloride (89 mg, 0.52 mmol) following the general procedure given above.

4.8.1. Data for *1,1′-methylenedi[(1*R*,1′*R*,3*R*,3′*R*,5*R*,5′*R*)-8-oxabicyclo[3.2.1]oct-6-en-3-yl] bis(*p*-methoxybenzoate)* **9**

^{1}H NMR (400 MHz, $CDCl_3$): 7.95 (d, 4H, $^3J=8.1$ Hz), 6.92 (d, 4H, $^3J=8.1$ Hz), 6.32 (d, 2H, $^3J=5.9$ Hz), 6.18 (dd, 2H, $^3J=5.9$, 1.5 Hz), 5.33 (br. dd, 2H, $^3J=6.0$, 5.9 Hz), 4.78 (br. d, 2H, $^3J=3.5$ Hz), 3.89 (s, 6H), 2.27 (br. ddd, 2H, $^2J=15.0$, $^3J=6.0$, 4.1 Hz), 2.16 (br. dd, 2H, $^2J=15.0$, $^3J=6.0$ Hz), 2.09 (br. s, 2H), 1.90 (br. d, 2H, $^2J=16.2$ Hz), 1.71 (br. d, 2H, $^2J=16.2$ Hz).

*4.8.2. Data for 1,1′-methylenedi[(3*S*,3′*S*,4*R*,4′*R*,6*S*,6′*S*)-3-chlorocyclohept-1-en-4,6-diyl] tetrakis(*p*-methoxybenzoate)* ***10***

^{1}H NMR (400 MHz, $CDCl_3$): 8.03 (d, 4H, $^3J=8.1$ Hz), 7.92 (d, 4H, $^3J=8.1$ Hz), 6.92 (d, 4H, $^3J=8.1$ Hz), 6.88 (d, 4H, $^3J=8.1$ Hz), 5.87 (d, 2H, $^3J=7.4$ Hz), 5.62 (br. d, 2H, $^3J=10.0$ Hz), 5.33 (m, 2H), 4.80 (br. d, 2H, $^3J=7.4$ Hz), 3.86 (s, 6H), 3.83 (s, 6H), 2.75 (m, 4H), 2.55 (br. dd, 2H, $^2J=12.5$, $^3J=7.6$ Hz), 2.35 (m, 2H), 2.19 (br. s, 2H).

*4.8.3. Data for 1,1′-methylenedi[(4*S*,4′*S*,6*S*,6′*S*)-cyclohept-1-en-4,6-diyl] tetrakis(paramethoxybenzoate) (+)-* ***11***

$[\alpha]^{25}_{589}=+186$, $[\alpha]^{25}_{577}=+208$, $[\alpha]^{25}_{546}=+227$, $[\alpha]^{25}_{435}=+441$, $[\alpha]^{25}_{403}=+584$ ($c=1.0$, $CHCl_3$). IR ($CHCl_3$): 2925, 2853, 1790, 1705, 1605, 1585 cm^{-1}; UV (CH_3CN): $\lambda_{max}=252$ nm, $\varepsilon=20\,000$. ^{1}H NMR ($CDCl_3$, 400 MHz): 7.99 (d, 4H, $^3J=8$ Hz), 7.97 (d, 4H, $^3J=8$ Hz), 6.91 (d, 4H, $^3J=8$ Hz), 6.89 (dd, 4H, $^3J=8$ Hz), 5.61 (dd, 2H, $^3J=6.0$, 5.9 Hz), 5.25 (m, 4H), 3.86 (s, 6H), 3.85 (s, 6H), 2.61 (m, 4H), 2.48 (m, 4H), 2.32 (m, 4H). ^{13}C NMR ($CDCl_3$, 100.6 MHz): 165.5, 165.4, 163.4, 137.6, 131.6, 123.7, 123.6, 122.9, 122.8, 113.6, 68.9, 68.8, 68.7, 68.6, 55.5, 55.4, 41.6, 35.7, 32.8, 29.7. MS (CI/NH_3): *m*/*z* 822 (16, [M+NH_4^+]), 653 (16), 642 (20), 338 (21), 265 (100), 135 (35), 83 (78). Anal. calcd for $C_{47}H_{48}O_{12}$: C, 70.14; H, 6.01. Found: C, 70.25; H, 6.23.

*4.8.4. Data for (−)-1,1′-methylenedi[(4*R*,4′*R*,6*R*,6′*R*)-cyclohept-1-en-4,6-diyl] tetrakis-(p-methoxybenzoate) (−)-* ***11***

$[\alpha]^{25}_{589}=-188$, $[\alpha]^{25}_{577}=-210$, $[\alpha]^{25}_{546}=-220$, $[\alpha]^{25}_{435}=-436$, $[\alpha]^{25}_{403}=-578$ ($c=1.0$, $CHCl_3$).

*4.8.5. Data for 1,1′-methylenedi[(3*S*,3′*S*,4*S*,4′*S*,6*S*,6′*S*)-6-acetoxy-3-chlorocyclohept-1-en-4-yl] bis(p-methoxybenzoate)* ***12***

^{1}H NMR (400 MHz, $CDCl_3$): 8.01 (d, 4H, $^3J=8.1$ Hz), 7.93 (d, 4H, $^3J=8.1$ Hz), 5.85 (d, 2H, $^3J=7.4$ Hz), 5.56 (br. d, 2H, $^3J=10.0$ Hz), 5.20 (m, 2H), 4.85 (br. d, 2H, $^3J=7.4$ Hz), 3.89 (s, 6H), 2.70 (m, 4H), 2.50 (br. dd, 2H, $^3J=12.5$, $^3J=7.6$ Hz), 2.25 (m, 2H), 2.07 (br. s, 6H), 2.06 (br. s, 2H).

*4.8.6. Data for 1,1′-methylenedi[(4*S*,4′*S*,6*S*,6′*S*)-6-acetoxycyclohept-1-en-4-yl] bis(p-methoxybenzoate)* ***13***

^{1}H NMR (400 MHz, $CDCl_3$): 8.01 (d, 4H, $^3J=8.0$ Hz), 7.93 (d, 4H, $^3J=8.0$ Hz), 5.57 (m, 2H), 5.28 (m, 2H), 5.05 (m, 2H), 3.89 (s, 6H), 2.71 (s, 2H), 2.58 (m, 4H), 2.39 (m, 4H), 2.27 (m, 4H).

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