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Tetrahedron: *Asymmetry* 16 (2005) 2277–2283

Enzymatic desymmetrization of 1,1′-methylenedi-[(1*R*,1′*S*,3*R*,3′*S*,5*S*,5′*R*)-3-hydroxy-8-oxabicyclo[3.2.1]-oct-6-ene-1-yl]: novel precursors of long chain polyketides

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Received 2 May 2005; accepted 25 May 2005
Available online 29 June 2005

Abstract—*meso*-1,1′-Methylenedi[(1*R*,1′*S*,3*R*,3′*S*,5*S*,5′*R*)-3-hydroxy-8-oxabicyclo[3.2.1]oct-6-ene-1-yl] **14** obtained through the [4+3]-cycloaddition of 2,2′-methylenedifuran to oxyallyl cation, followed by reduction, has been desymmetrized by means of a lipase catalyzed transesterification to afford (1*S*,3*S*,5*S*)-1-{[(1*R*,3*R*,5*R*)-3-hydroxy-8-oxabicyclo[3.2.1]oct-6-en-yl]methyl}-8-oxabicyclo[3.2.1]oct-6-en-3-yl acetate (−)-**15** (89% ee). This compound was transformed into aromatic ester derivatives for establishing the absolute configuration.

1. Introduction

Polyketides (1,3-polyoxo, 1,3-polyols, aldols) are amongst a great variety of natural products of biological interest[1] with several approaches for their syntheses already having been proposed.[2] Vogel et al. have developed a noniterative, asymmetric synthesis of fifteen-carbon polyketides, starting from the readily available 2,2′-methylenedifuran **1**. A double [4+3]-cycloaddition of halogenated 2-oxyallyl cations to **1** generates, after reductive work-up, a 55:45 mixture of diketones **2** and **3** (60% yield), which can be readily separated (Scheme 1).[3] Various pentadecan-1,3,5,7,9,11,13,15-octols were prepared from *meso*-**2**, using a late desymmetrization of diolefin **4** by means of the Sharpless asymmetric dihydroxylation.[4] It was reported that *threo*-**3** can be converted into the enantiomerically pure diacetate (+)-**8** and diol (−)-**7**,[5] and we have shown that they can be transformed in a few steps into enantiomerically pure, long-chain polyketides,[6] and polyfunctional 1,7-dioxaspiro[5.5]undecanes[7] as well. This efficient strategy is based on the double ozonolysis of dialkene (−)-**9** followed by the diastereoselective reduction of the resulting β-hydroxyketone intermediate to give rapid access to long-chain polyketides bearing unsymmetrical functions at the terminal positions, which can be further transformed into long chain 1,3-polyol fragments **12**. In order to generate more stereoisomeric 15-carbon polyketides it would be of high interest to achieve desymmetrization of the *meso* bicyclic adduct **2** in order to apply our double-ring opening pathway. Herein, we report a lipase-catalyzed transesterification for the desymmetrization[8] of diol **14**, readily obtained through the stereoselective reduction of **2** in the presence of K-selectride.

2. Results and discussion

Desymmetrization of diol **14** was attempted in the presence of several commercially available lipases (Scheme 2, Table 1), using vinyl acetate as solvent. Lipases from *Pseudomonas fluorescens*, *Pseudomonas cepacia*, *Aspergillus niger*, *Aspergillus orizae* and *Rizopus orizae* were uneffective in catalyzing the transesterification of **14** (entries 1–5). Lipase from *Candida rugosa* afforded a low conversion into the desired monoacetate (−)-**15** with an enantiomeric excess of 76%. Finally, lipase from *Candida cylindracea* afforded the monoacetate (−)-**15** with enantiomeric excesses ranging from 80% to 89%. The best results were obtained at 40 °C (10 h of reaction, 4000 U/mmol, 44% yield, 54% recovered starting diol). Elevation of the temperature (entry 10) or increasing

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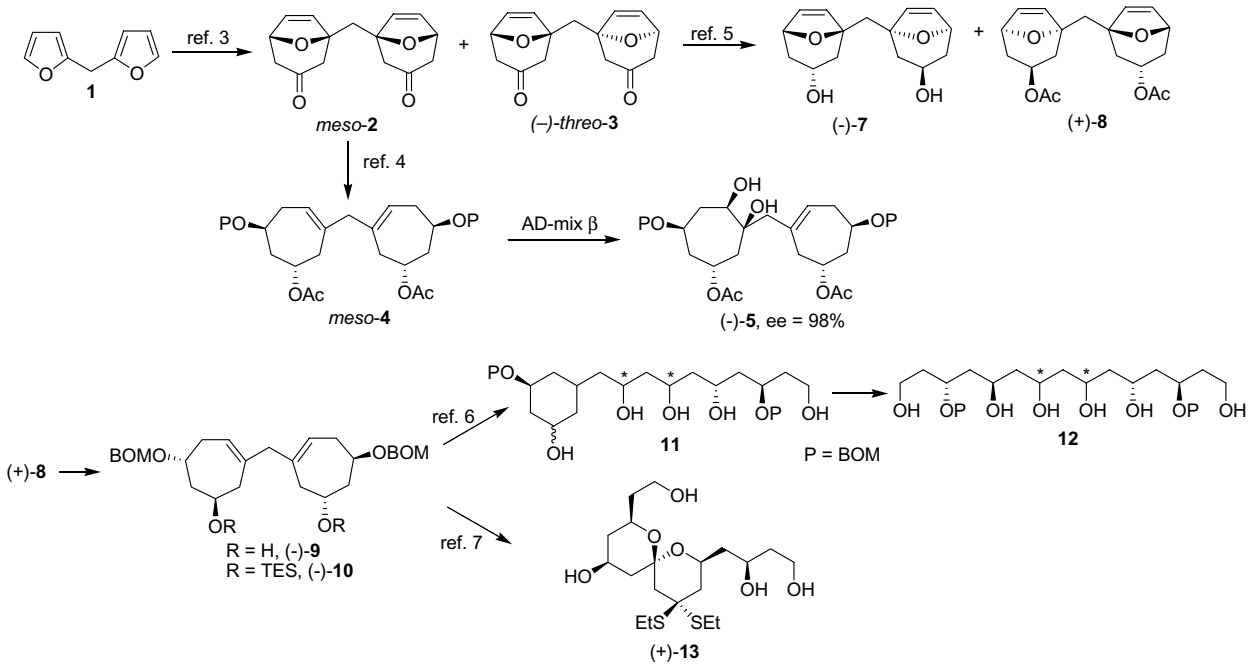
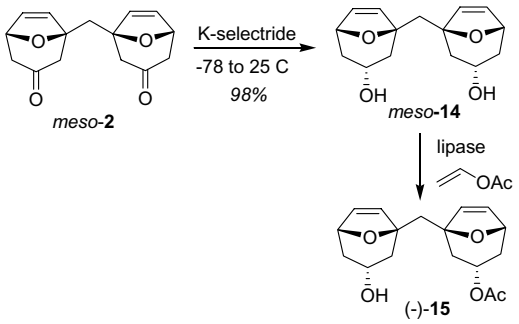
doi:10.1016/j.tetasy.2005.05.038



Scheme 1.



Scheme 2.

the amount of enzyme (entry 8) resulted in a loss of enantioselectivity. With the addition of cosolvents, such as toluene or chloroform, the transesterification did not occur (data not shown).

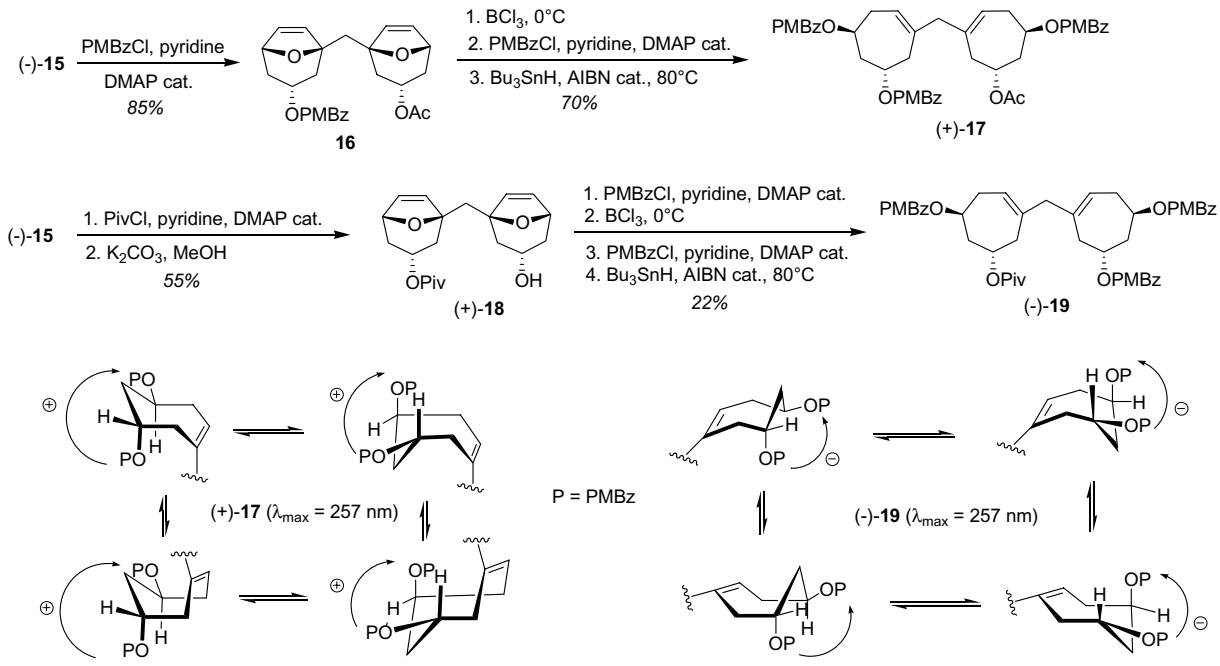
The absolute configuration of monoacetate (−)-**15** was determined by circular dichroism of tris(*para*-methoxybenzoate) (+)-**17** derived from (−)-**15** through a sequence involving transformations that do not modify the initial stereogenic centers (Scheme 3). Esterification of the free secondary alcohol in the presence of *para*-methoxybenzoyl chloride, followed by treatment with BCl_3 at 0 °C, protection of the resulting diol and reductive dechlorination (Bu_3SnH, AIBN) of the dichlorodiol intermediate, afforded derivative (+)-**17**, bearing *para*-methoxybenzoate chromophores. The complementary enantiomer was similarly obtained after introduction of a pivaloyl moiety on (−)-**15** and selective hydrolysis of the acetate at the C(3′) position.

A circular dichroism (CD) spectrum of (+)-**17** (Fig. 1) showed a double Cotton effect ($\Delta\varepsilon_{267} = +6$, $\Delta\varepsilon_{241} = -2$), which results from the exciton coupling between the two aromatic chromophores at C(4′) and C(6′) to produce a positive couplet.[9] This result was expected for all possible conformations of (+)-**17** (Scheme 3) and is consistent with the fact that the point of inflexion of the CD curve is close to $\lambda = 257$ nm, the

Table 1. Lipase catalyzed transesterification of **14**

Entry[a]	Lipase	U mmol^{-1}	Yield (−)-**15** (%)	ee[b] (%)	Yield (%), **14**	*T* (°C)
1	*Pseudomonas fluorescens*	4800	No reaction			25
2	*Pseudomonas cepacia*	14,400	No reaction			25
3	*Aspergillus niger*	3000	No reaction			25
4	*Aspergillus orizae*	4800	No reaction			25
5	*Rizopus orizae*	4800	No reaction			25
6	*Candida rugosa*	4800	17	76	56	25
7	*Candida cylindracea*	4000	44	85	46	25
8	*Candida cylindracea*	5800	34	80	46	25
9	*Candida cylindracea*	4000	44	89	54	40
10	*Candida cylindracea*	4000	40	81	38	60

[a] Assays were performed in 0.08 M of the solvent in vinyl acetate at 50 mg scale. Yields were calculated after isolation by flash chromatography.
[b] Determined by ^{1}H NMR of Mosher's ester.



Scheme 3.

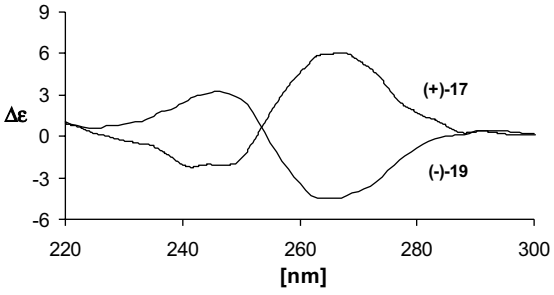


Figure 1. CD spectra of (+)-**17** and (−)-**19** in MeCN.

wavelength of maximum absorption in the UV spectrum. Furthermore, the circular dichroism (CD) spectrum of (−)-**19** (Fig. 1) showed a double Cotton effect ($\Delta\varepsilon_{264} = -4.5$, $\Delta\varepsilon_{246} = +3.2$) to produce a negative couplet, as expected for all possible conformations of this derivative. In this case, the point of inflexion of the CD curve is also close to $\lambda = 255$ nm, the wavelength of maximum absorption in the UV spectrum. These data allowed the establishment of the (1*R*,4′*S*,6*R*,6′*S*)- and the (1*S*,4′*R*,6*S*,6′*R*)-configurations of (+)-**17** and (−)-**19**, respectively, and thus the (1*S*,1′*R*,3*S*,3′*R*,5*S*,5′*R*)-configuration of monoacetate (−)-**15**.

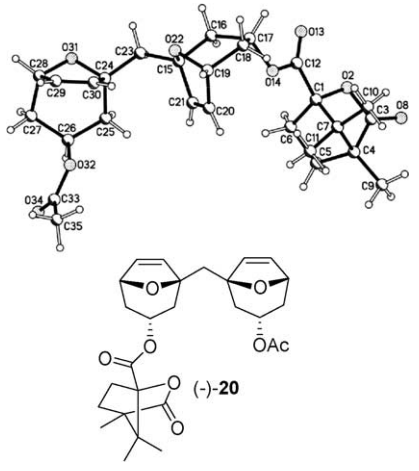


Figure 2. X-ray diffraction analysis of (−)-**20**.

This result was finally confirmed by X-ray crystallography of the (1*S*)-camphanoyl ester derivative of (−)-**15** (Fig. 2).[10]

3. Conclusion

We have demonstrated that *meso*-**14**, readily obtained from bicyclo adduct *meso*-**2**, can be desymmetrized at an early stage of its conversion into long-chain polyketides, affording (1*S*,3*S*,5*S*)-1-{[(1*R*,3*R*,5*R*)-3-hydroxy-8-oxabicyclo[3.2.1]oct-6-en-1-yl]methyl}-8-oxabicyclo[3.2.1]-oct-6-en-3-yl acetate (−)-**15** with 89% ee. This new derivative can be further transformed in order to introduce different functionalities on the two cycloheptene rings to provide new potential precursors of unsymmetrical long-chain polyketides.

4. Experimental

4.1. General

Commercial reagents (Fluka, Aldrich) were used without purification. Solvents were filtered prior to use (Innovative Technology). Solutions after reactions and extractions were evaporated in a rotatory evaporator under reduced pressure. Liquid/solid flash chromatography

(FC): columns of silica gel (0.040–0.63 mm, Merck No. 9385 silica gel 60, 240–400 mesh). TLC for reaction monitoring: Merck silica gel $60F_{254}$ plates; detection by UV light; Pancaldi reagent [$(NH_4)_6MoO_4$, $Ce(SO_4)_2$, H_2SO_4, H_2O]. IR spectra: Perkin–Elmer-1420 spectrometer. ^1H NMR spectra: Bruker-ARX-400 spectrometer (400 MHz); δ(H) in ppm relative to the solvent's residual ^1H signal [$CHCl_3$, δ(H) 7.27] as internal reference; all ^1H assignments were confirmed by 2D-COSY-45. ^{13}C NMR spectra: same instrument as above (100.6 MHz); δ(C) in ppm relative to solvent's C-signal [$CDCl_3$, δ(C) 77.0] as internal reference; coupling constants J in hertz. MALDI-TOF mass spectra were obtained from the Swiss Institute of Technology Mass Spectral Facility. Elemental analyses: Ilse Beetz, D-96301 Kronach, Germany. Circular dichroism spectra were recorded on a JOBIN YVON MARK VI using cubic quartz cell (length 0.1 cm) and calibrated with D-(+)-camphorsulfonic acid.

4.2. General procedure for the oxa-bridge opening and protection as *p*-methoxybenzoates

To a solution of the substrate (50–200 mg) in CH_2Cl_2 (2–8 mL) at 0 °C was added dropwise a 1 M solution of BCl_3 in CH_2Cl_2 (3 equiv). After stirring for 30 min at 0 °C, the mixture was poured into an aqueous saturated solution of $NaHCO_3$ (15 mL) and extracted with CH_2Cl_2 (3×15 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo. The residue was taken up in pyridine (3–5 mL) and treated with a catalytic amount of DMAP and *p*-methoxybenzoyl chloride (3 equiv). The resulting mixture was stirred at room temperature for 12 h. The solvent was evaporated under reduced pressure. The residue was taken up in an aqueous saturated solution of $NaHCO_3$ (10 mL) and extracted with DCM (3×10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash chromatography (30% AcOEt in pentane).

4.3. General procedure for the dechlorination

To a solution of the substrate (100 mg) in toluene (0.5 mL) were added Bu_3SnH (3 equiv) and a catalytic amount of AIBN. The mixture was stirred for 3 h at 80 °C. The solution was then diluted with CH_3CN (10 mL) and extracted with pentane (3×10 mL). The solution was concentrated in vacuo and the residue was purified by flash chromatography (30% AcOEt in pentane).

4.3.1. (1*S*,3*S*,5*S*)-1-{[(1*R*,3*R*,5*R*)-3-Hydroxy-8-oxabicyclo[3.2.1]oct-6-en-1-yl]methyl}-8-oxabicyclo[3.2.1]oct-6-en-3-yl acetate (−)-15. To a solution of diol **14** (140 mg, 0.530 mmol) in vinyl acetate (6.6 mL) at 40 °C was added lipase from *C. cylindracea* (2 U mg^{-1}, 4000 U $mmol^{-1}$, 1.06 g). The resulting suspension was stirred at 40 °C for 10 h. The mixture was filtered through a pad of Celite®. Removal of the solvent under reduced pressure and purification of the residue was done by flash chromatography (3–10% methanol in CH_2Cl_2) afforded (−)-**15** as a pale yellow oil (71 mg, 44%) and starting diol **14** as a pale yellow solid (76 mg, 54%). $[\alpha]_{405}^{23} = -20$, $[\alpha]_{435}^{23} = -19$, $[\alpha]_{577}^{23} = -9$, $[\alpha]_{589}^{23} = -8$ (*c* 0.46, $CHCl_3$). UV (CH_3CN): λ_{max} (ε) = 262, 228 (1624, 1363 $dm^3\ mol^{-1}\ cm^{-1}$) nm.

IR (film): 3450, 3075, 2940, 1345, 1255, 1225, 1030, 745, 700 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 6.49 (1H, d, ^3J = 5.9 Hz, H-7′), 6.36 (1H, dd, ^3J = 5.9, 1.6 Hz, H-6′), 6.15 (1H, d, ^3J = 6.0 Hz, H-7), 6.11 (1H, dd, ^3J = 6.0, 1.3 Hz, H-6), 5.05 (1H, t, ^3J = 5.8 Hz, H-3), 4.78 (1H, br s, H-5′), 4.76 (1H, br s, H-5), 3.97 (1H, m, H-3′), 2.25 (1H, d, ^3J = 10.4 Hz, OH–C-3′), 2.21–2.02 (2H, 2m, H-4$_{exo}$, H-4′$_{exo}$), 2.07 (1H, d, ^2J = 15.3 Hz, H-2$_{exo}$), 2.00 (1H, d, ^2J = 12.1 Hz, H-2′$_{exo}$), 1.98 (3H, s, CH_3(OAc)), 1.95 (2H, 2d, AB, ^2J = 14.5 Hz, H-8), 1.91 (1H, d, ^2J = 12.1, H-2′$_{endo}$), 1.72 (1H, d, ^2J = 15.3 H-2$_{endo}$), 1.68, 1.57 (2H, 2d, ^2J = 15.7, 10.6 Hz, H-4$_{endo}$, H-4′$_{endo}$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.4 (s, C=O), 138.8 (d, C$_{7'}$, $^1J_{C,H}$ = 168), 134.6 (d, C$_{6'}$, $^1J_{C,H}$ = 169), 136.5 (d, C$_7$, $^1J_{C,H}$ = 178), 132.5 (d, C$_6$, $^1J_{C,H}$ = 170), 84.3 (s, C$_{1'}$), 83.6 (s, C$_1$), 77.9 (d, C$_{5'}$), 77.8 (d, C$_5$), 67.2 (d, C$_{3'}$, $^1J_{C,H}$ = 161), 65.6 (d, C$_3$, $^1J_{C,H}$ = 142), 44.4 (t, C$_8$, $^1J_{C,H}$ = 123), 41.9 (d, C$_{2'}$, $^1J_{C,H}$ = 129), 38.0 (t, C$_2$, $^1J_{C,H}$ = 129), 31.7 (t, C$_4$, $^1J_{C,H}$ = 127), 35.5 (t, C$_{4'}$, $^1J_{C,H}$ = 125), 21.5 (q, CH_3-(OAc), $^1J_{C,H}$ = 127) ppm. MALDI-TOF: 329.46 (M+Na). Anal. Calcd for $C_{17}H_{22}O_5$ (306.36): C, 66.65; H, 7.24. Found C, 66.02; H, 7.28.

4.3.2. Data for (1*R*,6*R*)-6-(acetyloxy)-4-({(4*S*,6*S*)-4,6-bis[(4-methoxybenzoyl)oxy]cyclohept-1-en-yl}methyl)-cyclohept-3-en-1-yl 4-methoxybenzoate (+)-17. $[\alpha]_{405}^{23} = +154$, $[\alpha]_{435}^{23} = +116$, $[\alpha]_{577}^{23} = +50$, $[\alpha]_{589}^{23} = +44$ (*c* 0.47, $CHCl_3$). UV (CH_3CN): λ_{max} (ε) = 273, 266, 257 (34,000, 32,300, 34,880 $dm^3\ mol^{-1}\ cm^{-1}$) nm. IR (film): 3410, 2960, 2840, 1730, 1710, 1700, 1605, 1510, 1255, 1165, 1100, 1030, 850, 770, 695 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): 8.05–7.95 (m, 6H arom), 6.94–6.88 (m, 6H arom), 5.62 (1H, t, ^3J = 6.3 Hz, H-2′), 5.53 (H, t, ^3J = 6.5 Hz, H-3), 5.31 (2H, m, H-4′, H-1), 5.21, 5.02 (2H, 2m, H-6, H-6′), 3.85 (9H, s, 3OMe), 2.70 (2H, AB, ^2J = 14.2 Hz, H-8), 2.37, 2.19 (2×2H, 2t, ^3J = 5.6, 5.1 Hz, H-7, H-5′), 2.55 (2H, m, H-3′), 2.63–2.47 (2H, m, H-2), 2.63–2.52 (4H, m, H-5, H-7′), 1.99 (3H, s, CH_3(OAc)) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.2 (s, C=O(Ac)), 165.4, 165.3 (2s, 3C= O(PMBz)), 163.3, 163.2 (2s, C$_{arom}$), 137.6, 137.2 (2s, C$_{1'}$, C$_4$), 131.6, 131.5 (2d, C$_{arom}$, $^1J_{C,H}$ = 161, 162), 123.5, 123.4 (2d, C$_{2'}$, C$_3$, $^1J_{C,H}$ = 150.3), 122.9, 122.8, 122.7 (3s, C$_{arom}$), 113.6, 113.5 (2d, C$_{arom}$), 69.0, 68.9 (2d, C$_{4'}$, C$_1$, $^1J_{C,H}$ = 147), 68.4, 68.2 (2d, C$_6$, C$_{6'}$, $^1J_{C,H}$ = 148), 55.4, 55.3 (q, 3OMe, $^1J_{C,H}$ = 144), 50.5 (t, C$_{3'}$, C$_2$, $^1J_{C,H}$ = 122), 41.7, 41.5 (2t, C$_{5'}$, C$_7$, $^1J_{C,H}$ = 118, 125), 36.4 (t, C$_8$, $^1J_{C,H}$ = 124), 32.4, 32.1 (2t, C$_{7'}$, C$_5$, $^1J_{C,H}$ = 128, 127), 21.2 (q, CH_3(OAc), $^1J_{C,H}$ = 129) ppm. MALDI-TOF: 735.32 (M+Na), 751.28 (M+K). Anal. Calcd for $C_{41}H_{44}O_{11}$ (712.78): C, 69.09; H, 6.22. Found C, 69.07; H, 6.36.

4.3.3. (1*R*,3*R*,5*R*)-1-{[(1*S*,3*S*,5*S*)-3-Hydroxy-8-oxabicyclo[3.2.1]oct-6-en-1-yl]methyl}-8-oxabicyclo[3.2.1]oct-6-en-3-yl 2,2-dimethylpropanoate (+)-18. To a solution of alcohol (−)-**15** (710 mg, 0.232 mmol) in CH_2Cl_2/pyr-

idine (3/1, 8 mL) was added pivaloyl chloride (430 μL, 0.348 mmol). The resulting mixture was stirred at 25 °C for 12 h. The mixture was poured into an aqueous saturated solution of $NaHCO_3$ (15 mL) and extracted with CH_2Cl_2 (3 × 15mL). The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. Purification of the residue by flash chromatography (2% methanol in CH_2Cl_2) afforded a pivaloate intermediate as a colourless oil (615 mg, 68%). A solution of this intermediate (465 mg, 0.119 mmol) in methanol (6 mL) was treated with K_2CO_3 (250 mg, 0.179 mmol) for 12 h at 25 °C. The mixture was poured into an aqueous saturated solution of $NaHCO_3$ (10 mL) and extracted with AcOEt (3 × 10mL). The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. Purification of the residue by flash chromatography (2% methanol in CH_2Cl_2) afforded (+)-**18** as a white solid (338 mg, 81%). PF = 95 °C. $[\alpha]_{405}^{23} = +23$, $[\alpha]_{435}^{23} = +20$, $[\alpha]_{577}^{23} = +10$, $[\alpha]_{589}^{23} = +8$ (*c* 0.49, $CHCl_3$). UV (CH_3CN): λ_{max} (ε) = 228 (221 $dm^3\ mol^{-1}\ cm^{-1}$) nm. IR (KBr): 3590, 2941, 1720, 1655, 1560, 1460, 1290, 1165, 1030, 670 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 6.47 (1H, d, ^3J = 5.9 Hz, H-7′), 6.35 (1H, d, ^3J = 5.9 Hz, H-6′), 6.16 (1H, d, ^3J = 5.7 Hz, H-7), 6.11 (1H, d, ^3J = 5.7 Hz, H-6), 5.03 (1H, t, ^3J = 5.7 Hz, H-3), 4.76 (2H, br s, H-5, H-5′), 3.96 (1H, m, H-3′), 2.25 (1H, d, ^3J = 10.2 Hz, OH-C-3′), 2.16 (2H, 2dt, ^2J = 14.7, ^3J = 4.7 Hz, H-4$_{exo}$, H-4′$_{exo}$), 2.07 (2H, m, H-2$_{exo}$, H-2′$_{exo}$), 2.03 (2H, AB, ^2J = 15.0 Hz, H-8), 1.91 (1H, d, ^2J = 14.6 Hz, H-2′$_{endo}$), 1.67 (1H, d, ^2J = 14.8 Hz, H-2$_{endo}$), 1.67, 1.52 (2H, 2d, ^2J = 14.7 Hz, H-4$_{endo}$, H-4′$_{endo}$), 1.14 (9H, s, Me_3(Piv)) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.4 (s, C=O), 138.8 (d, $C_{7'}$, $^1J_{C,H}$ = 169), 136.5 (d, C_7, $^1J_{C,H}$ = 179), 134.6 (d, $C_{6'}$, $^1J_{C,H}$ = 170), 132.4 (d, C_6, $^1J_{C,H}$ = 170), 84.3, 83.8 (2s, C_1, $C_{1'}$), 78.0, 77.9 (2d, C_5, $C_{5'}$), 66.7 (d, $C_{3'}$, $^1J_{C,H}$ = 162), 65.6 (d, C_3, $^1J_{C,H}$ = 142), 44.4 (t, C_8, $^1J_{C,H}$ = 123.2), 41.9 (d, $C_{2'}$, $^1J_{C,H}$ = 129), 38.7 (s, $-C(Me)_3$), 38.1 (t, C_2, $^1J_{C,H}$ = 129), 35.6 (t, C_4, $^1J_{C,H}$ = 127), 31.7 (t, $C_{4'}$, $^1J_{C,H}$ = 125), 27.0 (q, $3CH_3$, $^1J_{C,H}$ = 127) ppm. MALDI-TOF: 371.5 (M+Na). Anal. Calcd for $C_{20}H_{28}O_5$ (348.43): C, 68.94; H, 8.10. Found C, 68.97; H, 8.03.

4.3.4. Data for (1*S*,6*S*)-4-({(4*R*,6*R*)-4,6-bis[(4-methoxybenzoyl)oxy]cyclohept-1-en-1-yl}methyl)-6-[(2,2-dimethylpropanoyl)oxy]cyclohept-3-en-1-yl 4-methoxybenzoate (−)-19. $[\alpha]_{405}^{23} = -116$, $[\alpha]_{435}^{23} = -88$, $[\alpha]_{589}^{23} = -35$ (*c* 0.55, $CHCl_3$). UV (CH_3CN): λ_{max} (ε) = 272, 267, 256 (34,000, 32,700, 36,885 $dm^3\ mol^{-1}\ cm^{-1}$) nm. IR (film): 2955, 1710, 1605, 1510, 1255, 1165, 1100, 1030, 845, 770, 695 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.06–7.94 (6H arom, m), 6.94–6.87 (6H arom, m), 5.59, 5.45 (2H, 2t, ^3J = 6.6, 6.9 Hz, H-2′, H-3), 5.32 (2H, m, H-1, H-4′), 5.18–5.01 (2H, 2m, H-6, H-6′), 3.86, 3.83 (9H, 2s, 3OMe), 2.87, 2.67 (2H, 2d, ^2J = 14.4 Hz, H-8), 2.64–2.40 (4H, m, H-5, H-7′), 2.57–2.37 (2H, m, H-2), 2.47–2.43, 2.38–2.35 (4H, 2m, H-7, H-5′), 2.38–2.35, 2.22–2.20 (4H, 2m, H-7, H-5′), 2.35 (2H, m, H-3′), 1.18 (9H, s, $3CH_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.6 (s, C=O(Piv)), 165.5, 165.4 (2s, 3C=O(PMBz)), 163.4, 163.3 (3s, C_{arom}), 137.6, 137.5 (2s, $C_{1'}$, C_4), 131.6, 131.5 (3d, C_{arom}, $^1J_{C,H}$ = 162, 161, 162), 123.4, 123.1 (2d, $C_{2'}$, C_3, $^1J_{C,H}$ = 150), 122.9, 122.8 (2s, C_{arom}), 113.6, 113.5 (2d, C_{arom}, $^1J_{C,H}$ = 160, 159), 69.1, 68.8 (2d, $C_{4'}$, C_1, $^1J_{C,H}$ = 147, 148), 68.6, 68.0 (2d, C_6, $C_{6'}$, $^1J_{C,H}$ = 146, 148), 55.4 (q, 3OMe, $^1J_{C,H}$ = 144), 50.6 (t, C_2, $C_{3'}$, $^1J_{C,H}$ = 122), 41.7, 41.4 (2t, $C_{5'}$, C_7, $^1J_{C,H}$ = 134), 32.6 (t, C_8, $^1J_{C,H}$ = 127), 38.7 (s, $C(Me)_3$), 36.4, 36.0 (2t, $C_{7'}$, C_5, $^1J_{C,H}$ = 128, 127), 26.8 (q, CH_3(Piv), $^1J_{C,H}$ = 127) ppm. MALDI-TOF: 777.74 (M+Na), 793.72 (M+K). Anal. Calcd for $C_{44}H_{50}O_{11}$ (754.34): C, 70.01; H, 6.68. Found C, 70.10; H, 6.70.

4.3.5. Mosher's ester of (−)-15. (1*R*,3*R*,5*R*)-1-{[(1*S*,3*S*,5*S*)-3-(Acetyloxy)-8-oxabicyclo[3.2.1]oct-6-en-1-yl]methyl}-8-oxabicyclo[3.2.1]oct-6-en-3-yl (2*S*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate. To a solution of (−)-**15** (10 mg, 0.033 mmol) in dichloromethane (0.5 mL) were added DMAP (2.5 mg, 0.020 mmol), pyridine (10 μL) and (1*S*)-(−)-α-methoxy-α-(trifluoromethyl)-phenylacetyl chloride (7 μL, 0.036 mmol). The resulting mixture was stirred at room temperature for 12 h. The mixture was poured into an aqueous saturated solution of $NaHCO_3$ (3 mL) and extracted with CH_2Cl_2 (3 × 3mL). The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. Purification of the residue by flash chromatography (3% methanol in CH_2Cl_2) afforded a colourless oil (9 mg, 96%). $[\alpha]_{405}^{23} = -55$, $[\alpha]_{435}^{23} = -45$, $[\alpha]_{577}^{23} = -24$, $[\alpha]_{589}^{23} = -26$ (*c* 0.65, $CHCl_3$). UV (CH_3CN): λ_{max} (ε) = 230, 261 (1088, 666 $dm^3\ mol^{-1}\ cm^{-1}$) nm. IR (film): 2920, 1730, 1680, 1454, 1360, 1255, 1185, 1120, 1030, 700 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.50–7.46, 7.43–7.37 ($5H_{arom}$, 2m), 6.16 (1H, d, ^3J = 6.0 Hz, H-6′), 6.11 (1H, dd, ^3J = 6.0, 1.6 Hz, H-7′), 5.85 (2H, s, H-6, H-7), 5.30, 5.03 (2H, 2t, ^3J = 5.1, 5.3 Hz, H-3′, H-3), 4.72 (2H, d, ^3J = 3.0 Hz, H-5, H-5′), 3.50 (3H, s, OMe), 2.23 (1H, ddd, ^2J = 15.2, ^3J = 5.1, 4.0 Hz, H-4′$_{exo}$), 2.14 (1H, ddd, ^2J = 15.0, ^3J = 5.3, 4.1 Hz, H-4$_{exo}$), 1.61, 1.55 (2H, 2d, ^2J = 15.2, 15.0 Hz, H-4′$_{endo}$, H-4$_{endo}$), 2.13 (1H, dd, ^2J = 15.2, ^3J = 6.0 Hz, H-2′$_{exo}$), 2.01 (2H, d, ^2J = 15.0, H-2$_{exo}$), 1.75, 1.71 (2H, 2d, ^2J = 15.2, 15.0, H-2′$_{endo}$, H-2$_{endo}$), 1.98 (2H, AB, ^2J = 15.0 Hz, H-8), 1.97 (3H, s, CH_3(OAc)) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): 170.4 (s, C=O(OAc)), 165.5 (s, C=O), 136.5 (d, $C_{7'}$, $^1J_{C,H}$ = 166), 136.3 (d, $C_{7'}$, $^1J_{C,H}$ = 166), 132.3 (d, $C_{6'}$, $^1J_{C,H}$ = 171), 131.9 (d, C_6, $^1J_{C,H}$ = 178), 129.5, 128.4, 127.3 (3d, C_{arom}, $^1J_{C,H}$ = 160, 159, 160), 124.8 (s, CF_3), 121.9 (s, $C(CF_3)$), 83.7, 83.6 (2s, $C_{1'}$, C_1), 77.7, 77.4 (2d, $C_{5'}$, C_5), 70.0 (2d, C_3, $C_{3'}$, $^1J_{C,H}$ = 152, 145), 55.2 (q, OMe, $^1J_{C,H}$ = 129), 44.1 (t, C_8, $^1J_{C,H}$ = 124), 38.0, 37.3 (2t, $C_{2'}$, C_2, $^1J_{C,H}$ = 127, 127), 31.6, 31.5 (2t, $C_{4'}$, C_4, $^1J_{C,H}$ = 128), 21.5 (q, CH_3(OAc), $^1J_{C,H}$ = 129) ppm. ^{19}F NMR (376.5 Hz, $CDCl_3$): −71.69 ppm. MALDI-TOF: 545.68 (M+Na). Anal. Calcd for $C_{27}H_{29}F_3O_7$ (522.51): C, 62.06; H, 5.59. Found C, 61.49; H, 5.64.

4.3.6. (1*R*,3*R*,5*R*)-1-{[(1*S*,3*S*,5*S*)-3-(Acetyloxy)-8-oxabicyclo[3.2.1]oct-6-en-1-yl]methyl}-8-oxabicyclo[3.2.1]-oct-6-en-3-yl 4,7,7-trimethyl-3-oxo-2-oxabicyclo[2.2.1]heptane-1-carboxylate (−)-20. To a solution of (−)-**15** (21 mg, 0.068 mmol) in dichloromethane (1 mL) were added DMAP (2.5 mg, 0.020 mmol), pyridine (100 μL)

and (1*S*)-(−)-camphanic chloride (23 mg, 0.103 mmol). The resulting mixture was stirred at 25 °C for 12 h. The mixture was poured into an aqueous saturated solution of $NaHCO_3$ (3 mL) and extracted with CH_2Cl_2 (3 × 3mL). The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. Purification of the residue by flash chromatography (3% methanol in CH_2Cl_2) afforded (−)-**20** as a colourless oil (34 mg, 96%). This oil crystallized as a white solid in pentane (3 mL) at 4 °C. PF: 162 °C. $[\alpha]_{405}^{23} = -8$, $[\alpha]_{435}^{23} = -6$, $[\alpha]_{589}^{23} = -3$ (*c* 0.24, $CHCl_3$). UV (CH_3CN): λ_{max} (ε) = 228 (1216 $dm^3\ mol^{-1}\ cm^{-1}$) nm. IR (KBr): 2960, 2845, 1715, 1700, 1610, 1505, 1420, 1290, 1160, 1120, 1035, 845, 770, 670 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): 6.19 (1H, d, $H_{7'}$, ^3J = 5.9 Hz, H-7′), 6.15 (2H, d, ^3J = 5.9 Hz, H-6′, H-7″), 6.09 (1H, dd, ^3J = 5.9, 1.0 Hz, H-6″), 5.22 (1H, t, ^3J = 5.9 Hz, H-3′), 5.03 (1H, t, ^3J = 5.7 Hz, H-3″), 4.75 (1H, br s, $H_{5'}$), 4.71 (1H, br s, $H_{5''}$), 2.37, 2.11 (2H, 2m, H-6_{exo}, H-6_{endo}), 2.22 (1H, m, H-$4'_{exo}$), 2.16–2.14 (1H, m, H-$4''_{exo}$), 2.12, 2.08 (2H, 2m, H-$2'_{exo}$, H-$2''_{exo}$), 2.00 (2H, 2d, ^2J = 14.7 Hz, H-8′), 1.97 (3H, s, CH_3(OAc)), 1.91, 1.68 (2H, 2m, H-5_{endo}, H-5_{exo}), 1.76, 1.71 (2H, 2dd, ^2J = 15.2, 14.8 Hz, H-$2'_{endo}$, H-$2''_{endo}$), 1.60, 1.55 (2H, 2d, ^2J = 15.5, 15.2 Hz, H-$4'_{endo}$, H-$4''_{endo}$), 1.11, 1.03, 0.93 (3 × 3H, 3s, $3CH_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.1 (s, C=O(camphanoyl)), 170.4 (s, C=O), 166.6 (s, C=O), 136.6 (d, $C_{7'}$, $^1J_{C,H}$ = 171), 136.5 (d, $C_{7''}$, $^1J_{C,H}$ = 171), 132.5 (d, $C_{6'}$, $^1J_{C,H}$ = 170), 132.3 (d, $C_{6''}$, $^1J_{C,H}$ = 170), 90.9 (s, C_7), 83.7, 83.6 (2s, $C_{1'}$, $C_{1'}$), 77.7, 77.4 (2d, $C_{5'}$, $C_{5''}$), 68.8 (d, $C_{3'}$, $^1J_{C,H}$ = 146), 67.2 (d, $C_{3''}$, $^1J_{C,H}$ = 151), 54.8, 54.1 (2s, C_1, C_4), 44.2 (t, $C_{8'}$, $^1J_{C,H}$ = 124), 38.0, 37.9 (2t, $C_{2'}$, $C_{2''}$, $^1J_{C,H}$ = 129), 31.7 (2t, $C_{4'}$, $C_{4''}$, $^1J_{C,H}$ = 128), 30.4 (t, C_6, $^1J_{C,H}$ = 128), 28.9 (t, C_5, $^1J_{C,H}$ = 136), 21.4 (q, CH_3(OAc), $^1J_{C,H}$ = 129), 16.9 (2q, $2CH_3$–C_7, $^1J_{C,H}$ = 127), 9.6 (q, CH_3–C_4, $^1J_{C,H}$ = 127) ppm. MALDI-TOF: 509.65 (M+Na). Anal. Calcd for $C_{27}H_{34}O_8$ (486.55): C, 66.65; H, 7.04. Found C, 66.65; H, 7.16.

Acknowledgements

This work was supported by the Swiss National Foundation (Grant No. 200020-100028/1). We thank Dr. Rosario Scopelitti for the X-ray analysis and Mr. Martial Rey, Mr. Mandal Bhubaneswar and Mr. Francisco Sepùlveda for technical help.

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10. Crystallographic data (excluding structure factors) for the structure herein have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 270615. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK.