Influence of Structural Factors and Enzyme Type on the Reactivity and Enantioselectivity of the Enzymatic Esterification of Bicyclic *meso* Dialcohols

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The *meso* dialcohols **1**–**7**, obtained from the Diels-Alder adducts furan/maleic anhydride, furan/dimethyl acetylenedicarboxylate, and cyclopentadiene/maleic anhydride, were subjected to enzymatic esterification in organic solvents. A mixture of the corresponding chiral monoacetates and the *meso* diacetates was obtained. It has been found that reaction rate and enantioselectivity markedly depend on substrate structure, temperature, enzyme type, and nature of the solvent. The presence of an oxygen bridge and an exo configuration are the two structural features which lead to the highest enantioselectivity values.

The stereocontrol in the formation of carbon-carbon bonds during the synthesis of chiral natural products has become of paramount importance in the last few decades. The high complexity of the molecules that organic chemists have been able to synthesize in recent times[1] has manifested itself in multi-step syntheses where only a high degree of stereochemical selection permitted to reach the desired target with an acceptable efficiency. Among the various synthetic methods employed, cycloaddition reactions have often played a main role in the armoury of the organic chemist, as they often generate several stereogenic centres in only one step, mostly with a high degree of diastereoselection[2].

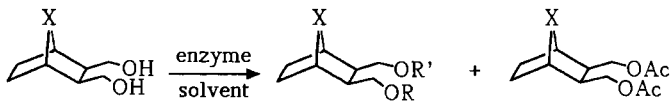
The last decade has witnessed an impressive increase in the use of biotransformations for synthetic purposes[3]. Most of these investigations have relied on the ability of enzymes to transfer their inherent chirality to organic substrates, i.e., to promote asymmetric syntheses with the formation of enantiomerically enriched products[4]. This goal has been actually achieved in a number of cases, especially with transacylation and redox reactions. Among the former, esterification reactions are particulary interesting for synthetic work, as they are performed in organic solvents, thus avoiding the necessity of using water as the reaction medium. Under these conditions, which are much more convenient for the organic chemist, both high chemical and stereochemical efficiency (enantiomeric excess, ee) have been reached in many cases[5].

The combination of the diastereoselectivity of cycloaddition reactions with the enantioselectivity of many enzymatic processes has developed into a powerful synthetic tool with a considerable potential for the synthesis of chiral organic products. This methodology, which represents an interesting, and in some cases cheaper, alternative to asymmetric cycloadditions with chiral auxiliaries[6], has already been successfully exploited by several groups[7–12].

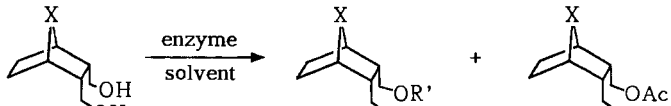
We have recently shown[13] that the combination of cycloaddition and enzymatic esterification may prove very efficient for the synthesis of chiral products. The *meso* dialcohols **1** and **3** (Scheme 1), obtained from known Diels-Alder adducts of furan, were subjected to enzymatic esterification with various enzyme/organic solvent combinations. Here the organic medium, which was either ethyl, vinyl, or isopropenyl acetate, acted as both the solvent and acylating agent. Under these combinations, the reactions are practically irreversible, as the great excess of acyl donor maintains the enzyme in the acylated form. Furthermore, in the case of enol esters, the tautomeric equilibrium continuously withdraws the hydroxylic enol form and prevents it from competing for the acyl moiety[5a].

We observed very high stereochemical efficiencies (99% ee) in the transformation of *exo* diol **1** to chiral monoacetate **8** (Scheme 1) when the combinations porcine pancreatic lipase/ethyl acetate (PPL/EA) or vinyl acetate (PPL/VA) were used[13]. The lipase from *Candida cylindracea* (CCL) proved also very efficient (96% ee) with isopropenyl acetate (IA). Interestingly, the chirality of the monoester obtained in this case was opposite to that of the product formed with PPL. The results observed with *endo* diol **3** (Scheme 1) were, how-

Scheme 1



1 X= O 8 X=O / R,R'=H,Ac 9 X = O
2 X= CH_2 10 X=CH_2 / R,R'=H,Ac 11 X= CH_2



3 X= O 12 X=O / R,R'=H,Ac 13 X= O
4 X= CH_2 14 X=CH_2 / R,R'=H,Ac 15 X= CH_2

ever, less satisfactory. Compound **3** behaved sluggishly in the acylation reaction, and only CCL and the more reactive ester VA could bring about the desired transformation with fair chemical yields and enantioselectivity (87% ee). It thus appears that the configuration of the substrate exerts a strong influence on both key features of the process.

In view of these results, we felt that a comparative study of the acylations of several related bicyclic substrates with various solvent/enzyme combinations at several temperatures would provide a clearer picture of the stereochemical preferences of the active site in the more commonly used enzymes PPL and CCL. Among other purposes, this also could help to predict the type of substrate most likely to yield good results in terms of both chemical yield and enantioselectivity. With this goal in mind, we prepared the *meso* dialcohols **2**, **4**, **5**, **6**, and **7**, easily obtained by appropriate transformation of the known Diels-Alder adducts of furan and cyclopentadiene with dimethyl acetylenedicarboxylate and maleic anhydride. Bicyclic compounds of this type have attracted interest as precursors for the synthesis of iridoids[14], nucleoside antibiotics[15], and prostaglandin and thromboxane analogues[16]. We now present the complete results of the enzymatic acylations of all these bicyclic dialcohols.

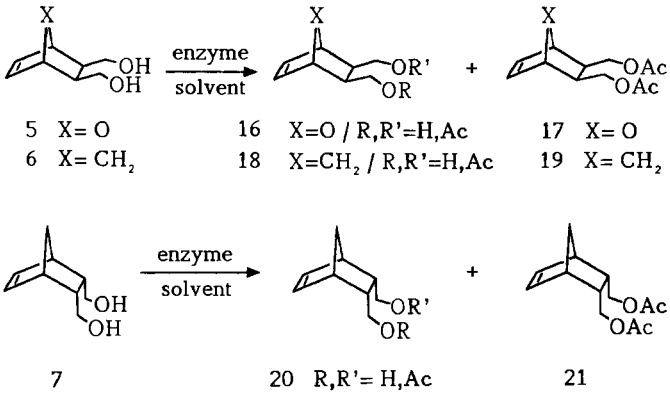
Enzyme-catalyzed acylation of the aforementioned symmetric *meso* diols gave rise to chiral monoacetates and *meso* diacetates (Schemes 1 and 2). The reaction was monitored at regular intervals by measurement of the optical rotation. A first maximum value was reached, which corresponds to the maximum yield in the chiral monoacetate and constitutes a measure of the enantiotoposelectivity of the enzyme, i.e., of its ability to select one of the enantiotopic hydroxymethyl groups. In some cases (entries 1, 10, 19 in Table 1), the optical rotation underwent a second, less pronounced

Table 1. Lipase-mediated acylation of bicyclic diols **1**–**7**

Entry	Comp.	Reaction conditions[a]	Starting diol[b]	Monoester				Diester[b]
				Comp.	% Yield	Ee[c]	$[\alpha]_D$[d]	
1	**1**	PPL / EA / 40 / 7 h	20	**8**	68	99	+15.4	12
2		PPL / VA / 20 / 50 min	–		92	99	+15.4	8
3		CCL / IA / 40 / 23 h	7		76	96	−14.6	17
4		CCL / VA / 20 / 20 min	18		70	76	−11.5	12
5	**2**	PPL / EA / 40 / 15 h	40	**10**	44	21	+3.9	16
6		CCL / IA / 40 / 18 h	59		39	8	+1.6	2
7	**3**	PPL / VA / 40 / 2 h	57	**12**	38	8	+1.0	5
8		CCL / VA / 20 / 50 min	–		72	87	+10.7	28
9		CCL / IA / 40 / 24 h	15		69	62	+7.6	16
10	**4**	PPL / VA / 40 / 24 h	16	**14**	52	16	+2.4	32
11		CCL / IA / 40 / 9 h	75		25	17	+2.6	–
12		CCL / VA / 20 / 20 min	28		62	52	+7.7	10
13	**5**	PPL / EA / 40 / 10 h	10	**16**	88	73	+6.8	2
14		PPL / VA / 20 / 2.5 h	3		93	79	+7.2	4
15		CCL / IA / 40 / 8 h	54		41	68	−6.3	5
16		CCL / VA / 20 / 30 min	6		64	62	−5.7	30
17	**6**	PPL / EA / 40 / 24 h	64	**18**	32	[e]	+0.9	4
18		CCL / IA / 40 / 20 h	42		48	[e]	+0.3	10
19	**7**	PPL / VA / 40 / 11 h	55	**20**	33	18	+3.8	12
20		CCL / IA / 40 / 6 h	62		33	14	+3.0	5
21		CCL / VA / 20 / 15 min	50		45	5	+1.1	5

[a] Lipase (porcine pancreatic lipase, PPL, or lipase from *Candida cylindracea*, CCL)/solvent (ethyl acetate, EA; vinyl acetate, VA; or isopropenyl acetate, IA)/temperature [°C]/time. – [b] Chemical yield (%). – [c] The enantiomeric excess (±1%) was determined by ^{1}H-NMR spectroscopy in the presence of Eu(hfc)$_3$. For the determination of the absolute configuration, see text. – [d] At 23°C (c = 1.5, EtOAc). – [e] ee was too low to be determined.

Scheme 2

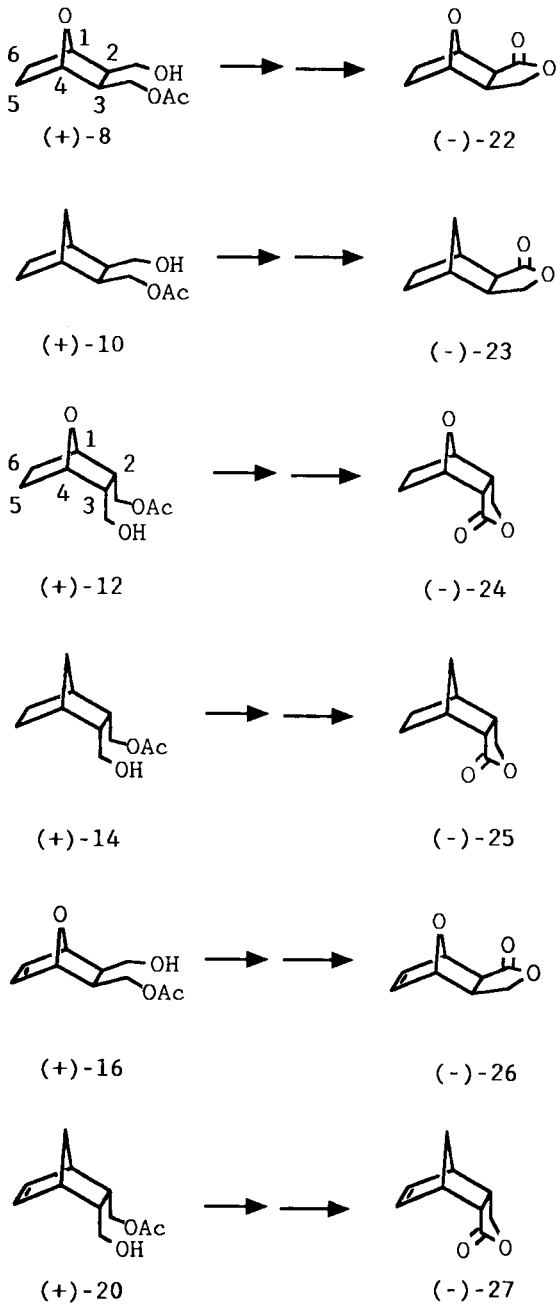


maximum value, which was due to the competition between the enantiotoposelectivity of the first step (diol → monoacetate) and the enantiomer differentiation during the second step (monoacetate → diacetate). In all cases, we stopped the reaction after the *first* maximum by filtration of the enzyme. Product distribution and enantiomeric purity of the obtained monoacetates are given in Table 1. The ee's range from the almost quantitative yield (99% ee) observed with the saturated *exo*-oxabicyclo diol **1**[13] (entries 1 and 2) to the negligible values of the unsaturated *exo*-norbornane derivative **6** (entries 17 and 18). A careful consideration of the values in Table 1 allows, however, the recognition of some regular trends. Oxabicyclic substrates, for instance, yield much higher ee's (>60%) than carbobicyclic ones (<55%), independently of the enzyme or solvent used (compare entries 1–4, 7–9, and 13–16 with 5–6, 10–12, and 17–21). The only exception is found in entry 7, which apparently corresponds to a particularly mismatched set of reaction conditions. Another distinct trend is the sensitivity of PPL to the relative configuration of the bridge and side chains (*exo* vs. *endo*). Only an *exo* configuration gives good results with this enzyme (compare entries 1, 2, 13, and 14 with 7, 10, and 19), whereas CCL shows comparatively little influence by this structural feature.

Further trends can also be observed in Table 1. As expected, vinyl esters are much more reactive than alkyl esters in acylation reactions. In fact, CCL works well only with vinyl esters (VA and IA), where it proves more reactive than PPL. Interestingly, no reaction is observed in the absence of enzyme. This contrasts with our recent observations in amino alcohols, where nonstereoselective *N*-acylation took place with enol esters even in the absence of enzyme, while *O*-acylation was observed with ethyl acetate and PPL[17]. It may also be worth mentioning that saturated substrates (**1**, **2**, and **4**) gave somewhat better results than their corresponding unsaturated counterparts (**5**, **6**, and **7**), independently of the reaction conditions. Less clear, however, is the overall influence of the spatial orientation of the side chains (*exo* vs. *endo*). As commented above, PPL is more sensitive than CCL to this structural aspect but it would seem that the latter may be outweighed by other features of the reaction (compare entries 17 and 18 with 8 and 12).

The ee's of the obtained monoacetates were measured by ^{1}H-NMR spectroscopy with the aid of the chiral additive Eu(hfc)$_3$. The absolute configurations were determined by oxidation of the primary alcohol group with Jones reagent, followed by saponification and acid treatment. This gave lactones **22**–**27** (Scheme 3), the optical rotations of which were compared with literature data[18] (the oxidation of ester **18** was not performed, because of the low value of its ee). The ee's deduced in this way for compounds **22**–**27** compared well with the values deduced from ^{1}H-NMR data for the precursor monoesters. An inspection of the molecular formulae in Scheme 3 reveals that both enzymes select the same half-space of the symmetry plane in all compounds

Scheme 3



belonging to the same stereochemical *exo* or *endo* series [as a consequence of the priority rules and of the configurational change, it is the (*S*)-CH_2OH which becomes acetylated in both the *exo* and the *endo* starting diols]. Compounds **1** and **5** constitute an exception to this trend, as PPL and CCL display opposite stereopreferences. It is also noteworthy that HLADH displays the same enantiotoposelectivity during the oxidation of the same substrates[18].

Some of the aforementioned chiral monoacetates have been previously obtained by enzyme-promoted reactions. This is, for instance, true of **16**, obtained in chiral form (absolute configuration unknown) by PLE-catalyzed hydrolysis of diacetate **17**[9]. The best ee reported by these authors was, however, 68%, to be compared with our best value of 79% (Table 1, entry 14). On the other hand, compound **20** has very recently been obtained by enzymatic acetylation of diol **7**[19]. By using lipase from *Geotrichum candidum*, these authors obtained an ee as high as 95%.

The results presented here are undoubtedly related to the structure of the active site in the corresponding enzyme. It is known that, among the various assayed enzymes, lipases are particularly stable in nonpolar solvents. They have the remarkable ability of assuming a variety of conformations to accommodate molecules of different size, which accounts for the broad spectrum of substrates they are able to accept[5a]. This is due to the considerable flexibility of their protein backbone, which allows for low energetic barriers during conformational transitions. Accurate three-dimensional X-ray data have only recently been published for the triacylglycerol lipase from *Mucor miehei* and for human pancreatic lipase[20]. It has been shown that an aspartic acid-histidine-serine triad is essential for the catalytic activity[5a,20].

Although the aforementioned flexibility of the enzyme may appear desirable, this has the main drawback that the resulting enantioselectivity is likely to vary within very broad ranges, from very high to almost zero, and that the stereochemical outcome of the reaction is difficult to predict. A further complicating fact is that cheap lipases, like those used in this work, are usually crude preparations with rather low activities. The presence of competing acylating enzymes in these crude preparations (e.g. proteases) should also be considered, since they may interfere in some cases by giving poor or even opposite stereoselectivity. In fact, it has recently been shown that the catalytic activity of crude PPL is actually due to minor components, which are not present in purified PPL[21]. Furthermore, it should be emphasized that the overall observed enantioselectivity is the average result, as commented in a preceeding paragraph, of *two consecutive and competitive steps:* the acylation of the achiral starting diol to the chiral monoacetate and the acylation of the latter to the achiral *meso* diacetate. Obviously, a good ee is the result of the co-occurrence of a high enzymatic enantiotoposelectivity in the first step and a high enantiodifferentiation *with the same stereopreference* in the second step. The absence of such cooperative effects might in part be the origin of the low enantioselectivity observed in some of our examples, but this point has not been investigated.

As a final remark, it may be concluded that the cavity in the active site of PPL has rather stringent stereochemical requirements for a good enantioselectivity to be obtained, as illustrated by the lower ee's observed in *endo* derivatives when compared with the corresponding *exo* compounds. The fact that carbobicyclic substrates are much worse substrates than the geometrically similar oxabicyclic counterparts may be due to the presence of an acidic centre in the active site, perhaps a serine residue, as commented before. This serine might bind the bridging oxygen atom of the oxabicylic substrates by means of a hydrogen bond. It may also be assumed that the active cavity of CCL has a different shape, as deduced from its different behaviour towards the same substrates, particularly from the intriguing fact that the acylation of diols **1** and **5** yielded in each case a monoacetate with a configuration opposite to that obtained in the PPL-catalyzed acylation (Table 1). It is worth mentioning that substrate models for both PPL and CCL, based on the results of hydrolyses of esters and of esterifications of alcohols, have recently been elaborated[10b,22]. While the models of PPL were based on studies with compounds very different of ours[22], the CCL model has been derived from results on hydrolysis of bicyclic esters[10b]. The conclusions drawn by these authors are not completely concurrent with our results, as they state, for instance, that an *endo*-configurated ester group must be present in order for a good enantioselectivity to be observed. Furthermore, the nature of the bridging atom does not seem to play a key role in their model, and the presence of C=C bonds may even be beneficial. This is precisely the opposite behaviour of that observed with our substrates, which are, of course, slightly different from those described in the mentioned paper[10b]. This means that either these small structural differences are decisive of the enantioselectivity of the process, or that the different reaction conditions (water vs. organic solvent) cause conformational changes in the enzyme and therefore a change in the topography of the active site. More work will be necessary to ascertain which of these two alternatives is the true one.

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Experimental

Melting points (uncorrected): Reichert apparatus. – IR (CCl_4 solution): Perkin-Elmer 843. – NMR: Bruker AC-200 ($CDCl_3$ solution with the solvent signal as reference). – MS: Hewlett-Packard 5988A (electron-impact mode, 70 eV). – Optical rotations: Perkin-Elmer polarimeter 241 (in EtOAc solution at 23°C). – Lipases (EC 3.1.1.3) PPL (Sigma type II, L 3126) and CCL (Sigma type VII, L 1754) were used as received.

meso Dialcohols **1**–**7** were prepared as described[16b,18].

Enzymatic Acylation of meso Dialcohols: The starting diol (1 g) was dissolved in the prescribed solvent (100 ml). PPL or CCL (2 g) was then added, and the mixture was stirred under the conditions of time and temperature given in Table 1. The course of the reaction was followed by monitoring the optical activity. When the *first*

maximum value was reached, the reaction was stopped by enzyme filtration. Removal of the solvent in vacuo yielded an oil, which was then subjected to column chromatography on silica gel (hexane/EtOAc, 5:3). Product distribution and yields are given in Table 1[23].

7-Oxabicyclo[2.2.1]heptane-exo-2,exo-3-dimethanol, Monoacetate (**8**): White solid, racemic form, m.p. 53–54°C; optically pure compound, m.p. 78–79°C (from hexane/EtOAc). – IR: $\tilde{\nu}$ = 3450 (OH), 1740 cm^{-1} (CO). – ^1H NMR: δ = 4.45, 4.37 (2 × t, *J* = 2.5 Hz, 2 × 1H, 1-, 4-H), 4.14 (dd, *J* = 10.8/5.5 Hz, 1H, C*H*OAc), 3.97 (dd, *J* = 10.8/9.2 Hz, C*H*OAc), 3.66 (dd, *J* = 10.3/5.6 Hz, 1H, C*H*OH), 3.55 (dd, *J* = 10.3/7.5 Hz, C*H*OH), 2.15 (m, 2H), 2.03 (s, 3H, OAc), 1.80 (m, 2H), 1.50 (m, 2H). – ^{13}C NMR: δ = 170.80 (s, acetate C=O), 79.08 (d, C-1, -4), 63.33 (t, CH_2OAc), 61.22 (t, CH_2OH), 48.50 (d, C-2), 45.50 (d, C-3), 29.38 (t, C-5, -6), 20.91 (q, acetate Me). – MS: *m/z* (%) = 169 (4) [M^+ – CH_2OH], 157 (10) [M^+ – $COCH_3$], 140 (8) [M^+ – HOAc], 122 (8) [M^+ – HOAc – H_2O], 109 (32), 97 (23), 96 (24), 95 (22), 94 (11), 93 (17), 87 (38), 85 (76), 83 (29), 81 (39), 79 (45), 69 (27), 68 (30), 67 (32), 43 (100).

7-Oxabicyclo[2.2.1]heptane-exo-2,exo-3-dimethanol, Diacetate (**9**): White solid, m.p. 102–103°C (from hexane/EtOAc) (ref.[24] 104–106.5°C). – IR: $\tilde{\nu}$ = 1740 cm^{-1} (CO). – ^1H NMR: δ = 4.41 (m, 2H, 1-, 4-H), 4.10 (dd, *J* = 10.8/5.6 Hz, 2H, 2 × C*H*OAc), 3.95 (dd, *J* = 10.8/9.1 Hz, 2H, 2 × C*H*OAc), 2.20 (m, 2H), 2.06 (s, 6H, 2 × OAc), 1.80 (m, 2H), 1.60–1.40 (m, 2H). – ^{13}C NMR: δ = 170.85 (s, acetate C=O), 78.77 (d, C-1, -4), 62.90 (t, CH_2OAc), 45.20 (d, C-2, -3), 29.24 (t, C-5, -6), 21.00 (q, acetate Me). – MS: *m/z* (%) = 199 (9) [M^+ – $COCH_3$], 183 (11) [M^+ – CH_3COO], 182 (5) [M^+ – HOAc], 169 (4) [M^+ – CH_2OAc], 122 (38) [M^+ – 2 HOAc], 109 (16), 95 (30), 81 (25), 79 (46), 43 (100).

Bicyclo[2.2.1]heptane-exo-2,exo-3-dimethanol, Monoacetate (**10**): Oil. – IR: $\tilde{\nu}$ = 3450 (OH), 1740 cm^{-1} (CO). – ^1H NMR: δ = 4.10 (dd, *J* = 11/6.2 Hz, 1H, C*H*OAc), 3.96 (dd, *J* = 11/7.5 Hz, 1H, C*H*OAc), 3.62 (dd, *J* = 11/6.2 Hz, 1H, C*H*OH), 3.48 (dd, *J* = 11/7.5 Hz, 1H, C*H*OH), 2.15 (m, 2H), 2.03 (s, 3H, OAc), 1.90 (m, 2H), 1.60–1.10 (m, 6H). – ^{13}C NMR: δ = 170.70 (s, acetate C=O), 64.65 (t, CH_2OAc), 62.63 (t, CH_2OH), 46.22 (d, C-2), 44.43 (d, C-3), 39.70, 39.44 (d, C-1, -4), 33.44 (t, C-7), 29.58, 29.31 (2 × t, C-5, -6), 21.00 (q, acetate Me). – MS: *m/z* (%) = 155 (5) [M^+ – $COCH_3$], 138 (13) [M^+ – HOAc], 137 (13) [M^+ – HOAc – H], 120 (18) [M^+ – HOAc – H_2O], 109 (31), 108 (40), 107 (38), 95 (18), 94 (29), 93 (19), 92 (18), 91 (29), 79 (100), 67 (39), 66 (49), 43 (70).

Bicyclo[2.2.1]heptane-exo-2,exo-3-dimethanol, Diacetate (**11**): Oil. – IR: $\tilde{\nu}$ = 1740 cm^{-1} (CO). – ^1H NMR: δ = 4.00 (m, 4H, 2 × CH_2OAc), 2.15 (m, 2H), 2.03 (s, 6H, 2 × OAc), 1.95 (m, 2H), 1.60–1.40 (m, 2H), 1.30–1.10 (m, 4H). – ^{13}C NMR: δ = 171.05 (s, acetate C=O), 64.32 (t, CH_2OAc), 44.23 (d, C-2, -3), 39.68 (d, C-1, -4), 33.32 (t, C-7), 29.31 (t, C-5, -6), 21.07 (q, acetate Me). – MS: *m/z* (%) = 181 (3) [M^+ – CH_3CO_2], 180 (1) [M^+ – HOAc], 120 (80) [M^+ – 2 HOAc], 107 (10), 105 (14), 94 (19), 93 (13), 92 (26), 91 (27), 79 (44), 67 (18), 66 (17), 43 (100).

7-Oxabicyclo[2.2.1]heptane-endo-2,endo-3-dimethanol, Monoacetate (**12**): White solid, racemic form, m.p. 53–54°C (from hexane/EtOAc). – IR: $\tilde{\nu}$ = 3450 (OH), 1740 cm^{-1} (CO). – ^1H NMR: δ = 4.58 (m, 2H, 1-, 4-H), 4.20 (dd, *J* = 11.3/6.8 Hz, 1H, C*H*OAc), 4.03 (dd, *J* = 11.3/8.6 Hz, 1H, C*H*OAc), 3.74 (dd, *J* = 10.7/7 Hz, 1H, C*H*OH), 3.58 (dd, *J* = 10.7/7.7 Hz, 1H, C*H*OH), 2.50 (m, 2H), 2.03 (s, 3H, OAc), 1.80–1.50 (m, 4H). – ^{13}C NMR: δ = 170.94 (s, acetate C=O), 79.38, 79.19 (2 × d, C-1, -4), 62.02 (t, CH_2OAc), 59.83 (t, CH_2OH), 44.54 (d, C-3), 40.89 (d, C-2), 24.18 (t, C-5, -6), 20.93 (q, acetate Me). – MS: *m/z* (%) = 169 (5) [M^+ – CH_2OH], 157 (12) [M^+ – $COCH_3$], 140 (8) [M^+ – HOAc], 122 (7) [M^+ – HOAc – H_2O], 109 (22), 97 (28), 96 (27), 95 (27), 93 (19), 87 (37), 85 (100), 83 (38), 81 (49), 79 (57), 69 (31), 68 (33), 67 (39), 43 (83).

7-Oxabicyclo[2.2.1]heptane-endo-2,endo-3-dimethanol, Diacetate (**13**): White solid, m.p. 92–93°C (from hexane/EtOAc). – IR: $\tilde{\nu}$ = 1740 cm^{-1} (CO). – ^1H NMR: δ = 4.52 (m, 2H, 1-, 4-H), 4.10 (dd, *J* = 11.2/7 Hz, 2H, 2 × C*H*OAc), 4.00 (dd, *J* = 11.2/9 Hz, 2H, 2 × C*H*OAc), 2.49 (m, 2H), 2.01 (s, 6H, 2 × OAc), 1.70–1.50 (m, 4H). – ^{13}C NMR: δ = 170.76 (s, acetate C=O), 79.15 (d, C-1, -4), 61.66 (t, CH_2OAc), 40.68 (d, C-2, -3), 24.12 (t, C-5, -6), 20.85 (q, acetate Me). – MS: *m/z* (%) = 199 (9) [M^+ – $COCH_3$], 183 (11) [M^+ – CH_3CO_2], 182 (4) [M^+ – HOAc], 169 (4) [M^+ – CH_2OAc], 140 (6) [M^+ – C_2H_2O – HOAc], 122 (35) [M^+ – 2 HOAc], 109 (9), 97 (13), 96 (16), 95 (26), 94 (21), 93 (26), 83 (19), 81 (25), 79 (45), 43 (100).

Bicyclo[2.2.1]heptane-endo-2,endo-3-dimethanol, Monoacetate (**14**): Oil. – IR: $\tilde{\nu}$ = 3450 (OH), 1740 cm^{-1} (CO). – ^1H NMR: δ = 4.06 (dd, *J* = 10.9/6 Hz, 1H, C*H*OAc), 3.90 (dd, *J* = 10.9/8.1 Hz, 1H, C*H*OAc), 3.52 (dd, *J* = 10.6/6.8 Hz, 1H, C*H*OH), 3.41 (dd, *J* = 10.6/7.7 Hz, 1H, C*H*OH), 2.10 (m, 4H), 1.87 (s, 3H, OAc), 1.40–1.10 (m, 6H). – ^{13}C NMR: δ = 171.24 (s, acetate C=O), 62.98 (t, CH_2OAc), 60.03 (t, CH_2OH), 42.51 (d, C-3), 39.40 (t, C-7), 39.57, 39.35, 38.92 (3 × d, C-1, -2, -4), 22.16, 22.08 (2 × t, C-5, -6), 20.84 (q, acetate Me). – MS: *m/z* (%) = 155 (2) [M^+ – $COCH_3$], 138 (19) [M^+ – HOAc], 137 (6) [M^+ – HOAc – H], 120 (33) [M^+ – HOAc – H_2O], 110 (19), 109 (42), 108 (18), 107 (53), 105 (21), 95 (17), 94 (17), 93 (18), 92 (27), 91 (35), 81 (21), 80 (29), 79 (100), 67 (39), 66 (36), 43 (82).

Bicyclo[2.2.1]heptane-endo-2,endo-3-dimethanol, Diacetate (**15**): White solid, m.p. 64–65°C (from hexane/EtOAc) (ref.[25a] 66°C). – IR: $\tilde{\nu}$ = 1740 cm^{-1} (CO). – ^1H NMR: δ = 4.02 (m, 4H, 2 × CH_2OAc), 2.22 (m, 4H), 1.96 (s, 6H, 2 × OAc), 1.40–1.10 (m, 6H). – ^{13}C NMR: δ = 170.93 (s, acetate C=O), 62.65 (t, CH_2OAc), 39.47 (t, C-7), 39.65, 39.04 (2 × d, C-1, -2, -3, -4), 22.19 (t, C-5, -6), 20.94 (q, acetate Me). – MS: *m/z* (%) = 181 (1) [M^+ – CH_3CO_2], 120 (100) [M^+ – 2 HOAc], 105 (19), 92 (30), 91 (35), 79 (21), 67 (11), 43 (73).

7-Oxabicyclo[2.2.1]hept-5-ene-exo-2,exo-3-dimethanol, Monoacetate (**16**): Oil (ref.[9] no physical data given). – IR: $\tilde{\nu}$ = 3450 (OH), 1740 cm^{-1} (CO). – ^1H NMR: δ = 6.37 (m, 2H, 5-, 6-H), 4.87, 4.78 (2 × br. s, 2H, 1-, 4-H), 4.29 (dd, *J* = 10.8/5.3 Hz, 1H, C*H*OAc), 3.99 (dd, *J* = 10.8/10.5 Hz, 1H, C*H*OAc), 3.79 (dd, *J* = 10.3/5.2 Hz, 1H, C*H*OH), 3.60 (dd, *J* = 10.3/10 Hz, 1H, C*H*OH), 2.06 (s, 3H, OAc), 2.00–1.80 (m, 2H). – ^{13}C NMR: δ = 170.55 (s, acetate C=O), 135.34, 134.47 (2 × d, C-5, -6), 79.81 (d, C-1, -4), 63.62 (t, CH_2OAc), 60.64 (t, CH_2OH), 41.81 (d, C-2), 38.42 (d, C-3), 20.30 (q, acetate Me). – MS: *m/z* (%) = 113 (7), 112 (15), 70 (68), 61 (5), 43 (100).

7-Oxabicyclo[2.2.1]hept-5-ene-exo-2,exo-3-dimethanol, Diacetate (**17**): White solid, m.p. 106–107°C (from hexane/EtOAc) (ref.[9] no physical data given). – IR: $\tilde{\nu}$ = 1740 cm^{-1} (CO). – ^1H NMR: δ = 6.36 (br. s, 2H, 5-, 6-H), 4.78 (br. s, 2H, 1-, 4-H), 4.27 (dd, *J* = 10.8/5.4 Hz, 2H, 2 × C*H*OAc), 3.99 (dd, *J* = 10.8/9.5 Hz, 2H, 2 × C*H*OAc), 2.07 (s, 6H, 2 × OAc), 2.00 (m, 2H). – ^{13}C NMR: δ = 170.35 (s, acetate C=O), 135.30 (d, C-5, -6), 80.19 (d, C-1, -4), 63.54 (t, CH_2OAc), 39.04 (d, C-2, -3), 20.56 (q, acetate Me). – MS: *m/z* (%) = 113 (15), 112 (28), 70 (77), 61 (5), 43 (100).

Bicyclo[2.2.1]hept-5-ene-exo-2,exo-3-dimethanol, Monoacetate (**18**): Oil. – IR: $\tilde{\nu}$ = 3450 (OH), 1740 cm^{-1} (CO). – ^1H NMR: δ = 6.15 (m, 2H, 5-, 6-H), 4.23 (dd, *J* = 11/6 Hz, 1H, C*H*OAc), 4.00 (dd, *J* = 11/8.5 Hz, 1H, C*H*OAc), 3.75 (dd, *J* = 10.6/6.3 Hz, 1H, C*H*OH), 3.50 (dd, *J* = 10.6/7.7 Hz, 1H, C*H*OH), 2.75 (m, 2H), 2.00 (s, 3H, OAc), 1.75 (m, 2H), 1.35 (m, 2H). – ^{13}C NMR: δ = 171.12 (s, acetate C=O), 137.52, 136.81 (2 × d, C-5, -6), 65.84 (t,

CH_2OAc), 63.49 (t, CH_2OH), 44.69, 44.40 (2 × d, C-1, -4), 43.19, 39.46 (2 × d, C-2, -3), 42.44 (t, C-7), 20.95 (q, acetate Me). – MS: *m/z* (%) = 196 (1) [M^+], 136 (1) [M^+ – HOAc], 131 (7), 113 (6), 91 (6), 79 (5), 71 (8), 66 (100), 43 (27).

Bicyclo[2.2.1]hept-5-ene-exo-2,exo-3-dimethanol, Diacetate (**19**): White solid, m.p. 49–50°C (from hexane/EtOAc). – IR: $\tilde{\nu}$ = 1740 cm^{-1} (CO). – ^1H NMR: δ = 6.18 (m, 2H, 5-, 6-H), 4.20 (dd, *J* = 11/5.8 Hz, 2H, 2 × C*H*OAc), 4.02 (dd, *J* = 11/8.5 Hz, 2H, 2 × C*H*OAc), 2.72 (m, 2H), 2.05 (s, 6H, 2 × OAc), 1.85 (m, 2H), 1.50–1.10 (m, 2H). – ^{13}C NMR: δ = 170.81 (s, acetate C=O), 137.27 (d, C-5, -6), 65.46 (t, CH_2OAc), 44.83 (d, C-1, -4), 42.50 (t, C-7), 39.76 (d, C-2, -3), 20.87 (q, acetate Me). – MS: *m/z* (%) = 178 (1) [M^+ – HOAc], 173 (8), 118 (6) [M^+ – 2 HOAc], 117 (6), 113 (42), 91 (6), 79 (4), 71 (8), 66 (100), 43 (33).

Bicyclo[2.2.1]hept-5-ene-endo-2,endo-3-dimethanol, Monoacetate (**20**): Oil, (ref.[19] no physical data given). – IR: $\tilde{\nu}$ = 3450 (OH), 1740 cm^{-1} (CO). – ^1H NMR: δ = 6.00 (m, 2H, 5-, 6-H), 3.75 (dd, *J* = 10.9/6 Hz, 1H, C*H*OAc), 3.51 (dd, *J* = 10.9/9.1 Hz, 1H, C*H*OAc), 3.21 (dd, *J* = 10.4/6.4 Hz, 1H, C*H*OH), 3.03 (dd, *J* = 10.4/8.3 Hz, 1H, C*H*OH), 2.75 (br. s, 1H), 2.68 (br. s, 1H), 2.25 (m, 2H), 1.85 (s, 3H, OAc), 1.40–1.10 (m, 2H). – ^{13}C NMR: δ = 171.15 (s, acetate C=O), 135.56, 134.79 (2 × d, C-5, -6), 64.85 (t, CH_2OAc), 61.69 (t, CH_2OH), 48.81 (t, C-7), 45.36, 45.18 (2 × d, C-1, -4), 44.14 (d, C-3), 40.26 (d, C-2), 20.79 (q, acetate Me). – MS: *m/z* (%) = 178 (1) [M^+ – H_2O], 136 (1) [M^+ – HOAc], 131 (6), 113 (5), 91 (4), 79 (4), 71 (7), 66 (100), 43 (12).

Bicyclo[2.2.1]hept-5-ene-endo-2,endo-3-dimethanol, Diacetate (**21**): White solid, m.p. 60–61°C (from hexane/EtOAc) (ref.[25b] 65°C). – IR: $\tilde{\nu}$ = 1740 cm^{-1} (CO). – ^1H NMR: δ = 6.14 (t, *J* = 1.8 Hz, 2H, 5-, 6-H), 3.88 (dd, *J* = 11/6.5 Hz, 2H, 2 × C*H*OAc), 3.76 (dd, *J* = 11/8.8 Hz, 2H, 2 × C*H*OAc), 2.90 (m, 2H), 2.50 (m, 2H), 2.03 (s, 6H, 2 × OAc), 1.60–1.20 (m, 2H). – ^{13}C NMR: δ = 170.90 (s, acetate C=O), 135.44 (d, C-5, -6), 64.57 (t, CH_2OAc), 49.01 (t, C-7), 45.53 (d, C-1, -4), 40.62 (d, C-2, -3), 21.00 (q, acetate Me). – MS: *m/z* (%) = 178 (2) [M^+ – HOAc], 173 (9), 136 (1) [M^+ – HOAc – C_2H_2O], 118 (6) [M^+ – 2 HOAc], 117 (6), 113 (42), 91 (6), 79 (4), 71 (7), 66 (100), 43 (30).

All new compounds listed above gave satisfactory elemental analyses (%C, ±0.4; %H, ±0.4).

Determination of the Absolute Configuration: Transformation of Monoacetates **8**, **10**, **12**, **14**, **16**, *and* **20** *to Lactones* **22**–**27**. – *General Procedure:* A solution of the monoester (1 mmol) in acetone (2 ml) was added dropwise at 0°C to a solution of Jones reagent (4 equiv.) in the same solvent (2 ml). After stirring at room temp. for 30 min, the reaction mixture was filtered through a pad of silica gel. The solvent was then evaporated in vacuo and the crude residue dissolved in MeOH (5 ml). After the addition of 1 M aqueous KOH (2 ml), the solution was refluxed for 2 h. The reaction mixture was then cooled, carefully acidified to pH 3–4, stirred for 5 min and extracted four times with EtOAc. The combined organic solutions were then dried with $MgSO_4$, and the solvent was evaporated in vacuo to yield the desired lactone.

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