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Chemistry of Insect Antifeedants from *Azadirachta Indica* (Part 17):[1] Synthesis of Model Compounds of Azadirachtin. Unusual Effect of Remote Substituents on the Course of the Oxidative Ring Contraction Reaction.

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Abstract: The synthesis of model compounds of azadirachtin containing the tetrahydrofuran-carboxylate hemiketal functional group was achieved. The course of the oxidative ring contraction reaction that was used to form this functional group was observed to be unusually sensitive to the nature of substituents remote from the reactive centre.

We have been interested in the chemistry and total synthesis of azadirachtin (**1**) for several years.[1,2] Recently we initiated a programme for the synthesis of model compounds of azadirachtin with a view to seeing if it was possible to make simple compounds that contained only part of the functionality of

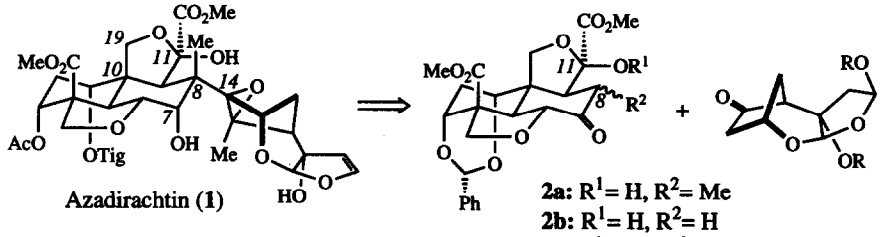


Figure 1

azadirachtin but displayed similar biological activity. Also, in connection with the total synthesis of azadirachtin,[2a,3] we wished to develop short, high-yielding, and general routes to compounds resembling the decalin portion of azadirachtin (**2a**) so that we could use these as models for the crucial C8-C14 coupling reaction that was central to our strategy (Figure 1). This paper describes our initial efforts in this area.

From recent structure-activity relationships (SAR) data, it appeared that the functionalities at the 7 and the 11 positions might have an important role to play in azadirachtin's biological effects.[2a,4] Also, because of the importance of compounds that would allow us to study model reactions for forming bonds at the C8 position of **2a**, we aimed to prepare a species that contained many of the important structural features of **2a**. Our initial target, therefore, was compound **3** (Figure 2). We envisioned that protection of the hemiketal OH of **3** would both provide us with an excellent model for coupling studies and also allow us to elaborate the 6-membered ring further to give compounds more closely related to the natural product.

Our general strategy for the preparation of **3** was based upon the one devised by our group during the synthesis of **2b**.[3] Specifically, we decided to introduce the tetrahydrofurancarboxylate hemiketal unit by means of an oxidative ring contraction of an α-cyano-δ-valerolactone such as compound **7**, which could be formed by

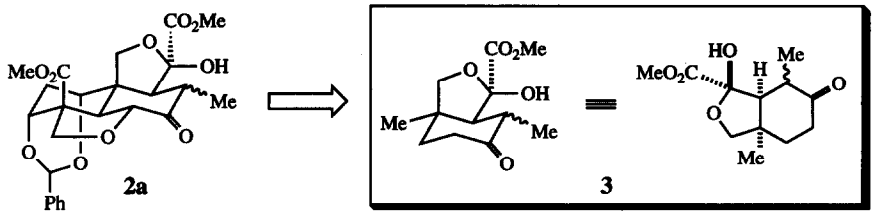
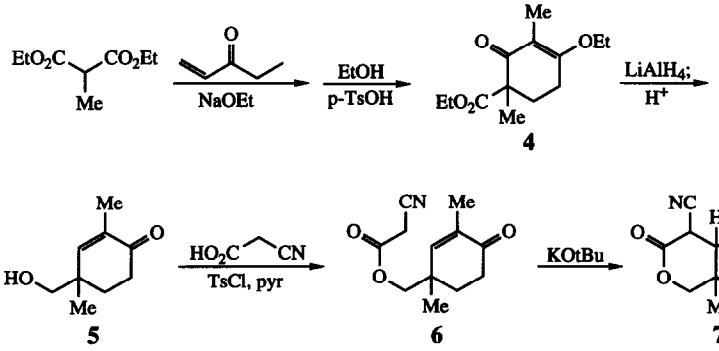


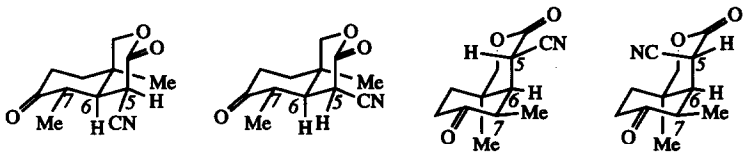
Figure 2



Scheme 1

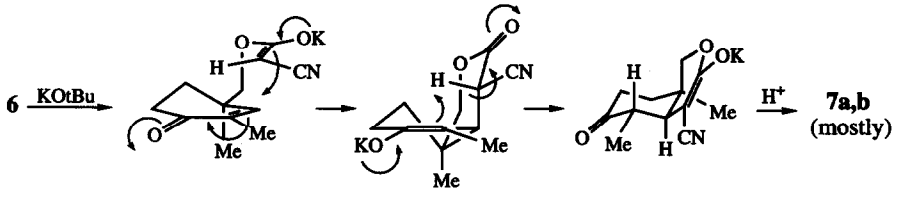
an intramolecular Michael addition reaction. In fact, addition of diethyl methylmalonate to ethyl vinyl ketone followed by intramolecular acylation of the ketone and formation of the enol ether gave β-alkoxyenone **4** in 24% overall yield (Scheme 1).[5] This was reduced with $LiAlH_4$ and hydrolyzed to give hydroxyenone **5** in 51% yield.[5] Compound **5** was acylated with cyanoacetic acid via the mixed anhydride with toluenesulfonic acid to give ester **6** (79% yield). Unlike the system described previously,[3] neither catalytic quantities of DBU nor stoichiometric amounts of LiHMDS effected cyclisation of **6**. However, it was found that treatment of **6** with a stoichiometric amount of *t*-BuOK in *t*-BuOH effected smooth cyclisation to give the bicyclic lactone **7** in 63% yield after recrystallisation from EtOH as a 7.5:6.5:1 inseparable mixture of diastereomers.

The stereochemistry of **7** is assigned using the following reasoning. Intramolecular Michael additions are known to give *cis* ring junctions,[6] and from this argument four structures (Figure 3) are theoretically possible, the conformation of each being determined by the configuration at C7. Structure **d** may be ruled out, owing to steric compression of the endo CN group. Structure **c** would be expected to show a large H5-H6 coupling constant due to the axial-axial interaction, whereas structures **a** and **b** should show smaller H5-H6 coupling constants. In fact, the minor diastereomer shows a coupling constant of 10.3 Hz, and the major ones show coupling constants of 5.9 and 6.3 Hz. Therefore the minor diastereomer is assigned as **c**, and the major products as **a** and **b**. The nearly equal amounts of **7a** and **7b** that are formed may reflect the fact that both have 1,3-diaxial interactions between the CN group and a Me group, and so are close in energy, or may simply



7a **7b** **7c** **7d**

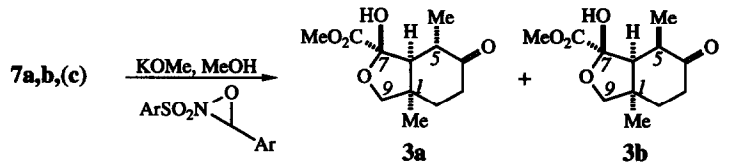
Figure 3



Scheme 2

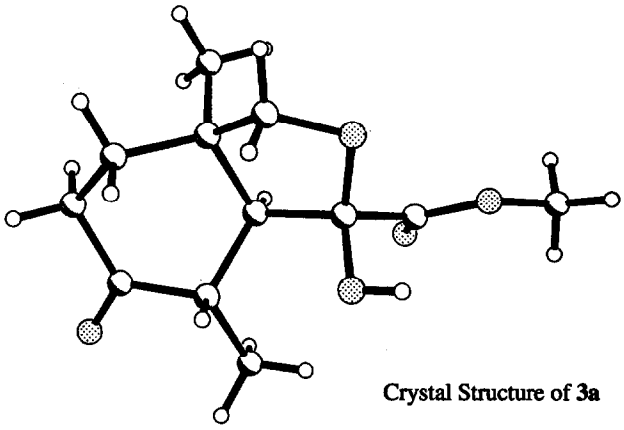
be a kinetic phenomenon of the final protonation step. The nearly homogeneous configuration at C7 is probably due to intramolecular H transfer from the cyanoester to the nascent enolate formed during the conjugate addition (Scheme 2).

The next step in the synthesis was the key oxidative ring contraction reaction, previously developed in these laboratories specifically for the formation of tetrahydrofurancarboxylate hemiketals.[3] To our surprise, however, neither mCPBA nor dimethyldioxirane was effective in the oxidation of the cyanolactone **7**,

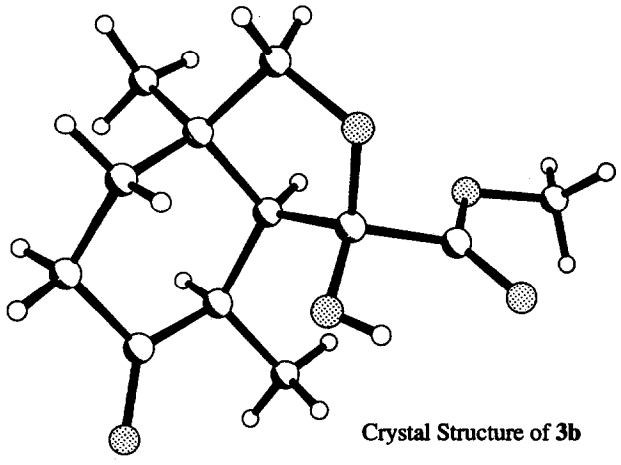


Scheme 3

despite the fact that both of these reagents worked well in the synthesis of **2b**. Fortunately, formation of the potassium enolate of **7** followed by treatment with two equivalents of Davis' oxaziridine reagent[7] in methanol at -78 °C and warming to room temperature gave the desired product **3** in >50% yield as an approximately 1:1 mixture of diastereomers (Scheme 3). The diastereomers **3a** and **3b** could be separated by chromatography, and as they were crystalline, X-ray analyses were conducted on each to establish their conformations and stereochemistries with certainty. The molecular structures of both are shown in Figure 4. The diastereomers differ only in their configuration at C5 (C8 in **1**), and they both display the configuration at C7 (C11 in **1**) that is found in the natural product, with the hemiketal OH group on the concave face of the bicyclic framework, in the thermodynamically favoured arrangement. The diastereomers assume conformations in which the C5 substituent is placed in an equatorial or bowsprit position, but neither diastereomer features an axial C1-C9 (C10-C19 in **1**) bond, as is seen in the natural product. The IR spectrum and the crystal structure of **3a** reveal an intermolecular hydrogen bonding interaction between the hydroxyl and the ketone (IR: 3251, 1688 cm^{-1}). This feature is completely absent in **3b** (IR: 3481, 1713 cm^{-1}). Compound **3a** showed no significant antifeedant activity against African leafworms, while **3b** showed borderline activity.[8]



Crystal Structure of **3a**



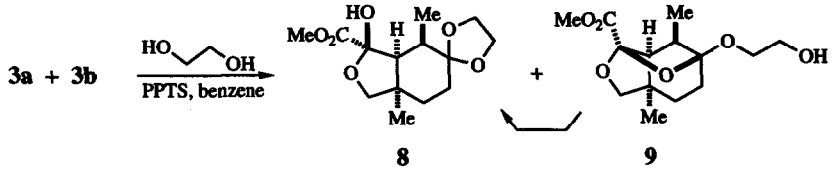
Crystal Structure of **3b**

Figure 4

With **3a** and **3b** in hand, our attention turned toward benzylation of the hydroxyl group and further functionalisation of the 6-membered ring. The benzylated product was particularly desirable as a model for C8-C14 coupling studies, because degradation of natural azadirachtin gave **2c** (Figure 1), which contained an 11-*O*-benzyl group.[2a,9] Benzylation of azadirachtin itself proceeded smoothly with benzyl bromide and silver(I) oxide,[9] but under these conditions both **3a** and **3b** gave a complex mixture of products. Neither benzyl trichloroacetimidate/ triflic acid[10] nor benzyl bromide/ NaH proved more satisfactory.

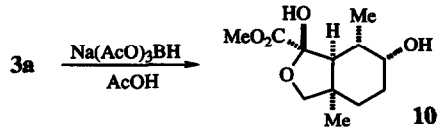
We thought that prior protection of the ketone as the ethylene ketal might facilitate benzylation of the hydroxyl group, but this turned out to be equally problematic. Treatment of a mixture of **3a** and **3b** with ethylene glycol and catalytic PPTS in benzene gave, in addition to starting material and many unidentified products, only small amounts of desired ketal **8** (ca. 13% yield) admixed with the interesting tricyclic isomer **9** (ca. 7% yield) and other products (Scheme 4). The compounds were identified by their distinctive NMR characteristics, and the structures were confirmed by mass spectroscopy. Neither compound was obtained in

pure form even after chromatography, and it was found that **9** slowly converted to **8**. The stereochemistry of **8** (and by analogy **9**) at C5 was assigned by comparison to its C5 epimer, **16a** (see below).



8 **9**

Scheme 4

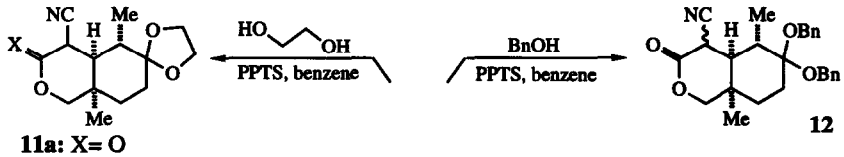


10

Scheme 5

Finally, reduction of **3a** with a large excess of $Na(AcO)_3BH$ in acetic acid[11] provided **10**, albeit in low yield and in impure form (Scheme 5). The stereochemistry was established by NOESY and COSY experiments. Use of smaller quantities of reducing agent resulted only in partial reaction. Attempted purification of **10** was unsuccessful; not only did chromatography fail to remove impurities, but use of EtOH in the eluant resulted in transesterification; when the ethyl ester was stirred over MeOH and silica, transesterification occurred again, but a new impurity appeared (see below). As expected, reduction of **3b** failed to proceed under these conditions.

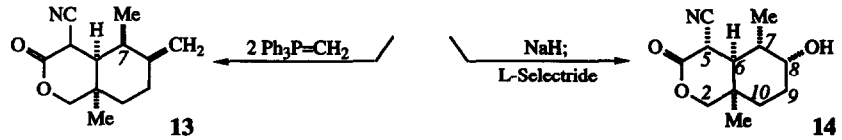
It occurred to us that protection or derivatisation of the ketone might be more facile if it was performed *before* the oxidative ring contraction step. Gratifyingly, formation of the ethylene ketal **11a**, the dibenzyl ketal **12**, the methylene compound **13**, and the alcohol **14** all proceeded smoothly (Scheme 6). Compound **11a** was obtained as a single diastereomer in 68% yield, along with another 14% of the orthoester **11b**, while **12** and **13** were obtained as 2:1 and 5.5:1 mixtures in 30% and 50% yields, respectively, and **14** was obtained as mostly a single diastereomer in 68% yield (ca. 90% pure). The stereochemistry of the major isomer of **13** was



11a: X= O
11b: X= $O(CH_2)_2O$

7a,b,(c)

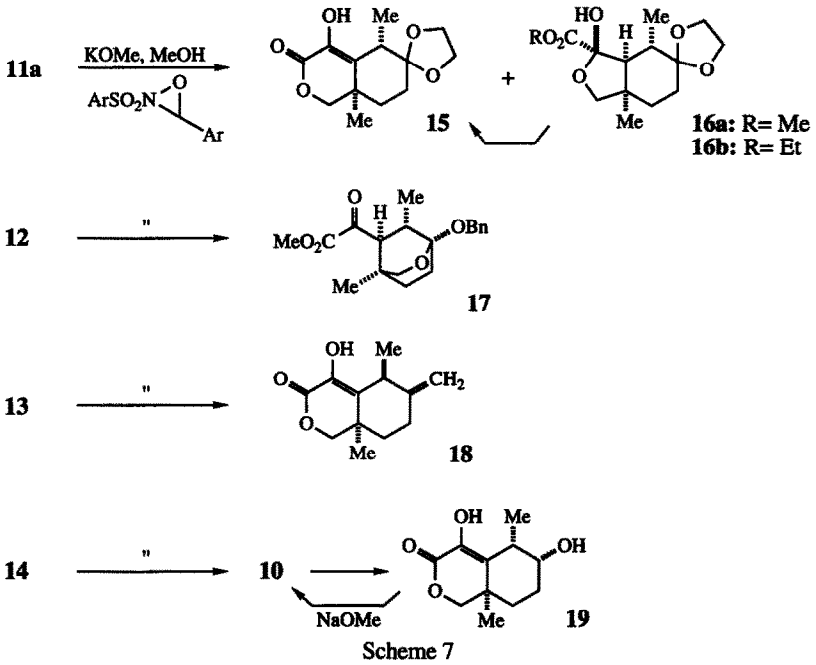
12



13 **14**

Scheme 6

inverted at C7 relative to that of the other compounds, as seen by the large H6-H7 coupling constant of 9.2 Hz (see discussion of **7** above). The stereochemistry of **14** at C5, C6 and C8 was established by NOESY and COSY experiments and by examination of coupling constants. Crucially, H8 showed small coupling constants to H7, H9α, and H9β, while it showed NOE's to all of the above and to the methyl group at C7. Moreover, H10α showed strong NOE to H6 but none to H8, and H9β, H7, and H2β showed strong NOE's among each other. Strong NOE was also observed between H5 and the methyl group at C7. These results fit a structure and conformation for **14** similar to the one shown for **7b** (Figure 3), with the ketone of course being replaced by an axial hydroxyl group.



Scheme 7

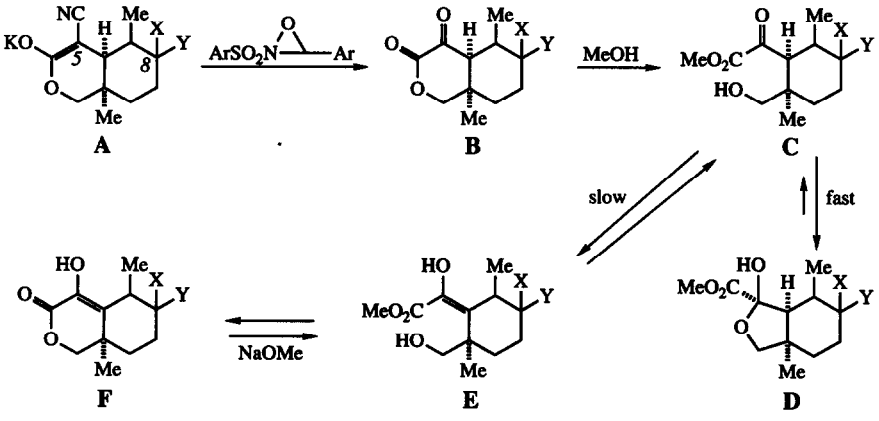
Compounds **11a-14** were subjected to the oxidative ring contraction reaction under the same conditions that gave rise to compound **3** (Scheme 7). To our surprise, in none of these cases was the major product the desired one. Upon oxidation of **11a,** the enol **15** was obtained in 58% yield. Very small amounts (ca. 1% yield) of the desired product **16a** were also obtained. These compounds co-eluted on silica gel in most solvent systems, but we were able to obtain **16** free from **15** by using EtOH/ petroleum ether as eluant. Under these conditions, though, **16a** transesterified to give **16b.** By stirring **16b** in methanol over silica, it was transesterified back to **16a** (homogeneous by TLC), but filtration and evaporation of solvent resulted in a 2.7:1 mixture of **16a** and **15** (^{1}H NMR in either $CDCl_3$ or CD_3OD). Conversion of **15** to the corresponding benzoate followed by refluxing in methanol with a catalytic amount of NaOMe also gave a mixture of **15** and **16a,** with **15** predominating. Clearly, the energies of **15** and **16** are finely balanced, but the barrier to interconversion seems to be low and the equilibrium seems to favour **15.**

The oxidations of **12** and **13** provided yet more surprising results. Compound **12** gave the remarkable bicyclo[2.2.2]octane compound **17** in 57% yield. The intramolecular transketalisation occurred under the non-

acidic reaction conditions. No other product was observed, and only a single diastereomer of **17** was obtained. The stereochemistry was established by NOESY and COSY experiments to be unchanged from **12.** Oxidation of **13,** on the other hand, gave the enol product **18** in 48% yield.

The oxidation of **14** provided a clue to the origin of this remarkable variation in the course of the reaction. TLC of the crude reaction mixture immediately after it had reached room temperature showed only one spot that was active to ammonium molybdate; this spot was not UV-active. After evaporation of solvent and flash chromatography, a single molybdate-active compound with a similar R_f was obtained, but it was now UV-active. Apparently, the UV-inactive hemiketal **10** had formed initially, but, upon removal of the alcohol solvent or during chromatography, it had rearranged to the enol **19.** The product **19** was obtained in 40% yield after two recrystallisations. Compound **19** was also latterly identified as the impurity that appeared during the chromatography of **10** that was obtained from reduction of **3a.** Partial conversion of **19** to **10** could be accomplished by heating **19** in MeOH with a catalytic amount of NaOMe, but **10** and **19** were inseparable by chromatography.

The question remains as to what causes the very similar compounds **7, 11a, 12, 13,** and **14** to give such a wide variety of products under the same reaction conditions. Our current hypothesis is as follows (Scheme 8). Oxidation of general structure **A** at C5 followed by elimination of cyanide gives the bicyclic α-ketoester **B,** which in all cases reacts with the solvent to give the monocyclic α-ketoester **C.** This compound is in equilibrium with the tetrahydrofurancarboxylate hemiketal **D,** with **D** being favoured. In cases where there is a strongly electron-withdrawing group at C8, the barrier for conversion of **D** back to **C** is high enough that **D** may be isolated. However, if the group at C8 is insufficiently electron-withdrawing, the



Scheme 8

equilibrium is shifted more favourably towards **C.** In this case, enolisation of **C** to give **E** is more likely to occur, and then **E** closes to give the observed product **F.** Conversion of **F** back to **E** and thence to **D** via **C** may be accomplished by treatment with basic NaOMe; the evidence also suggests that the reverse sequence of reactions may be catalyzed by silica and/or by removal of methanol. It is difficult to rationalise why, when X= Y= BnO, the product which is obtained is the bicyclo[2.2.2]octane **17.** It seems remarkable that an oxonium ion should form at C8 under these basic reaction conditions, and even more remarkable that the exchange of the solvent, methanol, with benzyl alcohol in such an ion should be much slower than opening of the hemiketal and

addition of the resulting alcohol to C8. It is possible that a solvent-assisted S_N2-like mechanism is operative,[12] and that it is thermodynamically and kinetically favourable because it allows the steric strain associated with the benzyl groups to be relieved.

The work that is described in this paper represents our first efforts in this area, and, although our initial results have not been as promising in all areas as we had originally hoped, they indicate the way by which more positive results may be obtained in the future. If we wish to devise a general route to models for azadirachtin, it will be necessary to eliminate the possibility of the formation of enol products in the oxidative ring contraction reaction. It has been pointed out that the C1-C9 bonds in **3a** and **3b** are equatorial or pseudo-equatorial with respect to the six-membered ring. If these bonds can be made to be axial, as they are in azadirachtin itself, the enol products will be unable to form, and the formation of the desired hemiketal may be favoured. We are currently working on systems in which this is the case, and our results will be reported in due course.

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Experimental Procedures.

All solvents were distilled before use. Petroleum ether refers to the 40-60 °C fraction. Proton and carbon NMR spectra were recorded on a Bruker AM-400, AC-250, AC-200, or DRX-500 spectrometer. NOESY and COSY spectra were recorded on a Bruker DRX-500 spectrometer. The residual solvent peaks were used as internal reference. ($CDCl_3$: δ 7.25 [^{1}H] or 77.0 [^{13}C] ppm; CD_3OD: δ 3.30 [^{1}H] or 49.0 [^{13}C] ppm.) Infrared spectra were recorded on a Perkin-Elmer FTIR 1620 spectrometer. Mass spectra were recorded on a Kratos MS890 spectrometer. Elemental analyses were conducted in the Microanalytical Laboratory in the Department of Chemistry, Cambridge. Flash chromatography was conducted on Merck Kieselgel 60 silica (230-400 mesh).

Results from the ^{13}C APT spectra are recorded after each ^{13}C resonance in the parentheses as "e" (even number of H atoms attached to the carbon in question), "quat" (quaternary carbon, as judged from the height of the peak), or "o" (odd number of H atoms). Where it is made, the assignment of each ^{1}H or ^{13}C resonance is written after each resonance, after the semi-colon inside the parentheses.

Ethyl 4-ethoxy-3,6-dimethyl-3-cyclohexen-2-one-1-carboxylate (4):[5] A solution of sodium (6.40 g, 0.28 mol) in anhydrous EtOH (ca. 400 mL) under Ar was slowly added via cannula to a solution of diethyl methylmalonate (43 mL, 0.25 mol) and ethyl vinyl ketone (25 mL, 0.25 mol) in anhydrous EtOH (ca. 100 mL) under Ar. An exothermic reaction occurred. When the addition was complete, the mixture was allowed to reflux overnight under a $CaCl_2$ drying tube. The solution was allowed to cool, and it was quenched with conc. HCl (25 mL). The solvent was evaporated. The residue was diluted with ether and water and shaken. The organic layer was shaken with water, then twice with brine, dried over $MgSO_4$, and evaporated. The viscous oil which was obtained was dried in vacuo, then redissolved in benzene (ca. 400 mL) and EtOH (50 mL). After adding *p*-toluenesulfonic acid monohydrate (1.87 g, 9.8 mmol), the mixture was brought to reflux under a Dean-Stark trap. After 5 h, 7.2 mL H_2O had accumulated. The mixture was allowed to cool, and it was

quenched with sat. aq. Na_2CO_3. The mixture was diluted with ether and water and shaken. The organic layer was shaken with brine, dried over $MgSO_4$, and evaporated. Vacuum distillation under a Vigreux column gave some starting material and decarboxylated product in the forerun, then **4** (bp 104 °C, 0.2 torr), but **4** distilled with another species, probably the regioisomer. Therefore the distillate was subjected to flash chromatography (25% EtOAc/ petroleum ether) to give pure **4** (14.54 g, 61 mmol, 24% yield) as a pale yellow liquid. ^{1}H NMR (250 MHz, $CDCl_3$): δ 4.12 (q, 7.1 Hz, 2H), 4.04 (m, 2H), 2.6-2.8 (m, 1H), 2.4-2.6 (m, 2H), 1.81 (m, 1H), 1.70 (t, 1.5 Hz, 3H), 1.35 (s, 3H), 1.33 (t, 7.0 Hz, 3H), 1.19 (t, 7.1 Hz, 3H). ^{13}C NMR + APT (100 MHz, $CDCl_3$): δ 196.0 (e), 173.0 (e), 169.8 (e), 114.0 (e), 63.4 (e), 61.1 (e), 51.5 (e, quat), 31.1 (e), 22.8 (e), 20.7 (o), 15.3 (o), 14.1 (o), 8.0 (o). IR (neat): 2981, 2935, 1729, 1650, 1617, 1446, 1380, 1351, 1237, 1205, 1180, 1121, 1014 cm^{-1}. Anal.: Calc. for $C_{13}H_{20}O_4$: C 64.98, H 8.39; found: C 64.93, H 8.40.

4-Hydroxymethyl-2,4-dimethyl-2-cyclohexen-1-one (5):[5] Compound **4** (18.63 g, 77.5 mmol) was slowly added to a solution of $LiAlH_4$ (4.42 g, 116 mmol) in ether (ca. 250 mL) at 0 °C. When the addition was complete, the suspension was allowed to warm to room temperature. After 2 h, the suspension was cooled back to 0 °C. Then water (4.4 mL), 15% aq. NaOH (4.4 mL), and water (13.2 mL) were slowly added (Fieser work-up).[13a] The suspension was filtered and evaporated. The liquid which was obtained was redissolved in THF (100 mL), and 1 *N* HCl (100 mL) was added. The reaction was allowed to stir overnight.[13b] The solution was then saturated with NaCl. The organic layer which separated was dried over $MgSO_4$ and evaporated. The material which was obtained was subjected to flash chromatography (50%, then 55% EtOAc/ petroleum ether) followed by Kugelrohr distillation to give **5** (6.10 g, 39.6 mmol, 51% yield) as a colourless liquid. This material was sufficiently pure to carry on to the next step. ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.46 (m, 1H), 3.49 (m, 2H), 2.48 (m, 1H), 2.06 (dt, J_d= 13.4 Hz, J_t= 7.5 Hz, 1H), 1.76 (m, 5H), including 1.76 (d, 1.5 Hz), 1.20 (t, 7.0 Hz, 1H), 1.13 (s, 3H). ^{13}C NMR + APT (100 MHz, $CDCl_3$): δ 199.7 (e), 150.7 (o), 135.3 (e), 70.2 (e), 38.3 (e, quat), 34.1 (e), 31.1 (e), 22.2 (o), 16.2 (o). IR (neat): 3432, 2926, 2868, 1672, 1450, 1365, 1050, 1017 cm^{-1}.

4-(2-Cyanoacetoxy)methyl-2,4-dimethyl-2-cyclohexen-1-one (6): *p*-Toluenesulfonyl chloride (7.63 g, 40.0 mmol) was added to a solution of **5** (3.08 g, 20.0 mmol), cyanoacetic acid (5.14 g, 60.4 mmol), and pyridine (11.4 mL, 141 mmol) in CH_2Cl_2 (ca. 150 mL). The reaction mixture slowly turned dark red. After 20 min, the mixture was diluted with EtOAc and water and shaken. The organic layer was shaken with dilute aq. NaCl, 1 *N* HCl, dilute aq. NaCl, and then brine. It was dried over $MgSO_4$ and evaporated. The residue was diluted with ether, filtered, and evaporated again. This material was twice subjected to flash chromatography (first time, 35%, then 40% EtOAc/ petroleum ether; second time, 30%, then 35% EtOAc/ petroleum ether) to give **6** (3.26 g, 14.7 mmol, 74% yield) as a pale yellow oil. ^{1}H NMR (250 MHz, $CDCl_3$): δ 6.38 (s, 1H), 4.09 (*AB*, 2H), 3.50 (s, 2H), 2.49 (apparent t, 7.4 Hz, 2H), 2.02 (m, 1H), 1.84 (m, 1H), 1.76 (d, 1.2 Hz, 3H), 1.19 (s, 3H). ^{13}C NMR + APT (100 MHz, $CDCl_3$): δ 198.7 (e), 162.9 (e), 148.1 (o), 136.1 (e), 112.8 (e), 72.5 (e), 36.8 (e, quat), 33.9 (e), 31.5 (e), 24.8 (e), 22.8 (o), 16.3 (o). IR (neat): 2964, 2263, 1747, 1682, 1454, 1371, 1336, 1264, 1180, 1089, 1010, 934, 884 cm^{-1}. HRMS: Calc. for $C_{12}H_{15}NO_3$: 221.1052; found: 221.1053.

***(1R*,5RS,6R,7S)*- and *(1R*,5S,6R,7R)*-5-Cyano-1,7-dimethyl-3-oxabicyclo[4.4.0]decane-4,8-dione (7):** A solution of **6** (4.06 g, 18.3 mmol) in dry *t*-BuOH (ca. 100 mL) under Ar was treated with KO-*t*-Bu (2.24 g, 20.0 mmol). A precipitate formed shortly. After 3 h, the reaction was quenched by the addition of 1 *N* HCl (22 mL). The solvent was evaporated. The residue was redissolved in CH_2Cl_2 and a little bit of water, and the mixture was shaken. The acidic aqueous layer was back-extracted with more CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and evaporated to give an orange solid. This was

recrystallised from hot EtOH at -20 °C to give 2.44 g **7**. The mother liquor was evaporated and subjected to flash chromatography (65% EtOAc/ petroleum ether) to provide a small amount more of **7**, which was also recrystallised from hot EtOH. Altogether, **7** was obtained (2.56 g, 11.5 mmol, 63% yield) as white crystals. According to NMR data, ca. 7.5:6.5:1 mixture of diastereomers was obtained. Resonances due to the minor diastereomer are presented in {braces}. ^{1}H NMR (250 MHz, $CDCl_3$): δ 4.62 (d, 12.3 Hz), 4.27 (d, 12.0 Hz), {4.20 (d, 11.7 Hz,)}, 4.19 (d, 12.0 Hz), 4.10 (d, 12.3 Hz), {4.08 (d, 11.7 Hz)}, altogether 2H. δ 3.80 (d, 5.9 Hz), 3.59 (d, 6.3 Hz,), {3.21 (d, 10.3 Hz)}, altogether 1H. δ {3.08 (dq, J_d= J_q= 6.8 Hz)}, 2.82 (dq, 5-6 Hz), 2.5 (m, all isomers), 2.20 (m, 1H of one isomer), 2.00 (m, 1H of 2 isomers), 1.63 (m, all isomers), altogether 6H. δ 1.24 (d, 6.6 Hz), 1.23 (s), 1.12 (s), 1.11 (d, partly obscured), altogether 6H. ^{13}C NMR + APT (100 MHz, $CDCl_3$): δ 209.7 (e), 208.9 (e), 163.8 (e), 163.2 (e), 115.4 (e), 113.2 (e), 76.0 (e), 74.6 (e), {49.8 (o)}, 47.8 (o), 46.3 (o), 44.9 (o), {43.6 (o)}, 43.4 (o), 36.4 (o), {36.3 (?)}, 35.4 (o), 34.3 (e), 34.2 (e), 34.1 (e, quat), 33.9 (e, quat), {33.3 (o)}, {29.6 (e)}, 29.0 (e), 28.4 (e), 26.0 (o), 24.8 (o), {22.4 (o)}, 12.5 (o), 11.7 (o), {9.2 (o).} IR (Nujol): 2253 (v. weak), 1738 (doubled), 1715, 1172 cm^{-1}. Anal.: Calc. for $C_{12}H_{15}NO_3$: C 65.14, H 6.83, N 6.33; found: C 65.05, H 6.89, N 6.31.

Methyl *(1R*,5S,6S,7S)-* and *(1R*,5R,6S,7S)*-7-hydroxy-1,5-dimethyl-8-oxabicyclo[4.3.0]-nonan-4-one-7-carboxylate (3a and 3b): A suspension of **7** (443 mg, 2.00 mmol) in dry methanol (40 mL) under Ar was treated with KO-*t*-Bu (248 mg, 2.21 mmol). The solid dissolved completely, and a light yellow colour developed. The solution was cooled to -78 °C, and 2-(4-methoxybenzenesulfonyl)-3-(4-nitrophenyl)oxaziridine[7] (1.48 g, 4.40 mmol) was added. The suspension was allowed to warm to room temperature. As it warmed, the oxaziridine slowly dissolved, and the reaction mixture turned dark red. After stirring at room temperature for 1 h, the solvent was evaporated on the rotary evaporator. Some CH_2Cl_2 was added and evaporated to remove residual methanol. The mixture was twice subjected to flash chromatography (first time, 35%, then 40% EtOAc/ petroleum ether; second time, 10%, then 12% ether/ CH_2Cl_2) to give **3** (279 mg, 1.15 mmol, 58% yield) as a yellow oil of ca. 92% purity by ^{1}H NMR. A major contaminant was 4-methoxybenzenesulfonamide.

In an earlier preparation of **3**, in which only one equivalent of oxaziridine was used, repeated chromatographic purifications followed by recrystallisation from slowly evaporating ether/ heptane achieved the separation of **3a** (larger R_f) and **3b** from each other and from the impurities. In this way, starting with 743 mg of **7**, **3a** was obtained (80 mg, 0.33 mmol, 10% yield) as off-white prisms, mp. 105-106 °C, and **3b** was obtained (121 mg, 0.50 mmol, 15% yield) as off-white needles, mp. 110-111 °C. The stereochemistries were determined by X-ray crystallographic analysis of each diastereomer. **3a:** ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.13 (d, 0.9 Hz, 1H; OH), 3.89 (d, 8.5 Hz, 1H; 9a), 3.83 (s, 3H; Me ester), 3.81 (d, 8.6 Hz, 1H; 9b), 2.76 (dq, J_d= 8.6 Hz, J_q= 6.7 Hz, 1H; 5), 2.2-2.5 (m, 4H; 2a, 3, 6), 1.70 (dt, J_d= 13.0 Hz, J_t= 4.2 Hz, 1H; 2b), 1.20 (s, 3H; 11), 0.98 (d, 6.7 Hz, 3H; 12). ^{13}C NMR + APT (100 MHz, $CDCl_3$): δ 213.8 (e), 171.3 (e), 103.0 (e), 80.5 (e), 58.2 (o), 53.6 (o), 41.6 (o), 40.3 (e, quat), 34.6 (e), 30.7 (e), 26.4 (o), 14.2 (o). IR (nujol): 3251 (sharp), 1748, 1688, 1234, 1102, 1060, 1015 cm^{-1}. Anal.: Calc. for $C_{12}H_{18}O_5$: C 59.49, H 7.49; found: C 59.30, H 7.51. **3b:** ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.20 (d, 1.4 Hz, 1H; OH), 3.92 (d, 8.3 Hz, 1H; 9a), 3.82 (s, 3H; Me ester), 3.72 (d, 8.3 Hz, 1H; 9b), 2.85 (d, 6.1 Hz, 1H; 6); 2.3-2.6 (m, 4H; 2a, 3, 5), 1.70 (m, 1H; 2b), 1.35 (s, 3H; 11), 0.98 (d, 6.8 Hz, 3H; 12). ^{13}C NMR + APT (100 MHz, $CDCl_3$): δ 210.6 (e), 171.7 (e), 102.2 (e), 79.5 (e), 57.7 (o), 53.5 (o), 40.3 (e, quat), 39.8 (o), 36.3 (e), 23.9 (o), 11.4 (o). IR (Nujol): 3481, 1725, 1713, 1294, 1260, 1180, 1144, 1097, 1018 cm^{-1}. Anal.: Calc. for $C_{12}H_{18}O_5$: C 59.49, H 7.49; found: C 59.37, H 7.59.

Crystal Data for 3a: Single crystals of **3a** were grown from slowly evaporating ether/ heptane. $C_{12}H_{18}O_5$, M= 242.3, monoclinic, space group $P2_1/c$, a= 12.093(2), b= 7.748(2), c= 14.003(3) Å, α= 90, β= 110.19(3),

γ= 90°, V= 1231.4(5) Å^3, Z= 4, D_c= 1.307 Mg/m^3, λ= 0.71073 Å, μ(Mo-Kα)= 0.101 mm^{-1}, F(000)= 520. Data were measured on a Siemens-Stoe AED four circle diffractometer using a crystal of dimensions 0.47 × 0.46 × 0.31 mm by the θ/ω method (3.05° ≤ θ ≤ 22.54°). Of a total of 1768 collected reflections, 1626 were unique. The structure was solved by direct methods (SHELX TL PLUS) and refined by the full-matrix least-squares method (SHELXL-93)[14] on F^2 to $R1$= 0.056 [F> 4σ(F)] and w$R2$= 0.1515 (all data) [$R1$= Σ| |F_o|- |F_c| |/ Σ|F_o|, $R2$= $\sqrt{\{\Sigma w(F_o^2 - F_c^2)^2 / \Sigma w F_o^4\}}$, w= [$\sigma^2(F_o^2)$+ (xP)^2+ yP]$^{-1}$, P= ($F_o^2$+ 2$F_c^2$)/3. The hydrogen atom of the hydroxy group was located directly from the difference map. All other hydrogen atoms were idealised and allowed to ride on their parent carbon atoms. The maximum and minimum residual electron densities in the final ΔF map were 0.385 and -0.236 eÅ^{-3}, respectively. Full details have been deposited at the Cambridge Crystallographic Data Centre.

Crystal Data for 3b: Single crystals of **3b** were grown from slowly evaporating toluene. $C_{12}H_{18}O_5$, M= 242.3, monoclinic, space group C2/c, a= 25.948(5), b= 5.9170(10), c= 15.422(3) Å, α= 90, β= 93.28(3), γ= 90°, V= 2363.9(8) Å^3, Z= 8, D_c= 1.361 Mg/m^3, λ= 0.71073 Å, μ(Mo-Kα)= 0.105 mm^{-1}, F(000)= 1040. Data were measured on a Siemens-Stoe AED four circle diffractometer using a crystal of dimensions 0.32 × 0.26 × 0.21 mm by the θ/ω method (3.53° ≤ θ ≤ 22.50°). Of a total of 1589 collected reflections, 1550 were unique. The structure was solved by direct methods (SHELX TL PLUS) and refined by the full-matrix least-squares method (SHELXL-93)[14] on F^2 to $R1$= 0.046 [F> 4σ(F)] and w$R2$= 0.1611 (all data) [$R1$= Σ| |F_o|- |F_c| |/ Σ|F_o|, $R2$= $\sqrt{\{\Sigma w(F_o^2 - F_c^2)^2 / \Sigma w F_o^4\}}$, w= [$\sigma^2(F_o^2)$+ (xP)^2+ yP]$^{-1}$, P= ($F_o^2$+ 2$F_c^2$)/3. All hydrogen atoms were idealised and allowed to ride on their parent carbon atoms. The maximum and minimum residual electron densities in the final ΔF map were 0.502 and -0.487 eÅ^{-3}, respectively. Full details have been deposited at the Cambridge Crystallographic Data Centre.

Methyl *(1R*,5R,6S,7S)*-4-spiro-2'-(1',3'-dioxolane)-7-hydroxy-1,5-dimethyl-8-oxabicyclo[4.3.0]nonane-7-carboxylate (8) and methyl *(1S*,4R,7R,8S,9R)*-1-(2-hydroxyethyl)-4,9-dimethyl-6,10-dioxatricyclo[5.2.1.0^{4,8}]decane-7-carboxylate (9): A solution of **3a** and **3b** (348 mg of ca. 92% purity, 1.44 mmol, ca. 1:1 mixture), ethylene glycol (140 mg, 2.25 mmol), and pyridinium *p*-toluenesulfonate (20 mg, 0.08 mmol) in benzene (ca. 40 mL) was allowed to reflux under a Dean-Stark trap overnight. The solvent was evaporated. Flash chromatography (40%, then 50%, then 60%, then 70% ethyl acetate/ petroleum ether) afforded **3a** and **3b** (161 mg, 46% recovery), impure **8** (52 mg, 0.18 mmol, ca. 13% yield), and impure **9** (29 mg, 0.10 mmol, ca. 7% yield) as oils. The impure **9** was rechromatographed (2.5% EtOH/ $CHCl_2$) three weeks later to afford slightly cleaner **9** (14 mg) and **8** (8 mg) as oils; the **8** had not been present after the first chromatography. **8:** ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.09 (s, 1H), 4.04 (m, 4H), 3.78 (s + d, 8.4 Hz, 4H), 3.59 (d, 8.4 Hz, 1H), 2.78 (dd, 6.7 Hz, 1.6 Hz, 1H), 2.27 (quintet, 7.2 Hz, 1H), 2.06 (dt, J_t= 14.2 Hz, J_d= 3.9 Hz, 1H), 1.74 (dt, J_d= 13.6 Hz, J_t= 3.6 Hz, 1H), 1.67 (dt, partly obscured by H_2O, J_t= 14.2 Hz, J_d= 3.8 Hz, 1H), 1.47 (dm, J_d= 14.0 Hz, 1H), 1.14 (s, 3H), 1.05 (d, 7.2 Hz, 3H). ^{13}C NMR + APT (100 MHz, $CDCl_3$): δ 172.2 (e), 109.7 (e), 103.7 (e), 79.0 (e), 66.2 (e), 65.1 (e), 55.6 (o), 52.8 (o), 40.1 (e, quat), 35.6 (o), 31.6 (e), 31.0 (e), 21.6 (o), 10.3 (o). IR (neat): 3354, 2955, 2885, 1738, 1462, 1256, 1112, 1044, 1010 cm^{-1}. HRMS: Calc. for $C_{14}H_{22}O_6$: 286.1416; found: 286.1418. **9:** ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.90 (m, 2H), 3.65-3.85 (m, 7H; includes δ 3.78 [s]), 2.77 (v. broad, 1H), 2.62 (s, 1H), 2.27 (m, 2H), 2.00 (m, 1H), 1.58 (m, 2H), 1.16 (s, 3H), 0.93 (d, 7.0 Hz, 3H). ^{13}C NMR + APT (100 MHz, $CDCl_3$): δ 169.2 (e), 110.3 (e), 110.0 (e), 82.4 (e), 65.6 (e), 62.3 (e), 60.2 (o), 52.8 (o), 42.0 (e, quat), 38.8 (o), 32.8 (e), 31.6 (e), 25.6 (o), 12.1 (o). IR (neat): 3500, 2954, 2875, 1747, 1463, 1341, 1289, 1272, 1224, 1201, 1176, 1144, 1061, 982, 900, 857, 734 cm^{-1}. HRMS: Calc. for $C_{14}H_{22}O_6$: 286.1416; found: 286.1415.

Methyl *(1R*,4R,5S,6S,7S)*-4,7-dihydroxy-1,5-dimethyl-8-oxabicyclo[4.3.0]nonane-7-carboxylate (10): Acetic acid (6 mL) was added to a mixture of **3a** (48 mg, 200 μmol) and sodium triacetoxyborohydride (213 mg, 1010 μmol). Both solids dissolved after a few minutes. After 1 h, a second batch of reducing agent (108 mg, 510 μmol) were added. After 80 min, the reaction was poured into a mixture of EtOAc and sat. aq. Na_2CO_3, and the mixture was shaken. The aqueous layer was back-extracted with EtOAc, and the combined organic layers were shaken once more with sat. aq. Na_2CO_3, which was back-extracted again with EtOAc. The combined organic layers were dried over $MgSO_4$ and evaporated. Flash chromatography was conducted twice (first time, 60% EtOAc/ petroleum ether; second time, 55% EtOAc/ petroleum ether) to afford **10** (6 mg, 25 μmol, 12% yield) as an oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.27 (dt, J_d= 9.7 Hz, J_t= 5.3 Hz, 1H), 4.27 (s, 1H), 3.83 (s, 3H), 3.74 (d, 8.2 Hz, 1H), 3.62 (d, 8.2 Hz, 1H), 2.35 (s, 1H), 2.03 (m, 1H), 1.86 (dt, J_t= 12.9 Hz, J_d= 4.6 Hz, 1H), 1.6-1.7 (m, 2H), 1.48 (dm, J_d=13.3 Hz, 1H), 1.20 (s, 3H), 1.06 (d, 7.4 Hz, 3H). ^{13}C NMR + APT (100 MHz, $CDCl_3$): δ 172.7 (e), 104.1 (e), 80.5 (e), 70.0 (o), 56.1 (o), 53.5 (o), 39.3 (e, quat), 32.5 (o), 32.3 (e), 26.2 (e), 24.7 (o), 14.8 (o). The assignments and stereochemistry were confirmed by NOESY and COSY experiments. Compound **10** was also prepared by heating **19** (see below) (23 mg, 110 μmol) at 75 °C overnight in methanol (ca. 0.8 mL) to which sodium (0.6 mg, 30 μmol) had been added. The reaction was quenched with solid NH_4Cl, and the solvent was evaporated. Extraction of the solid with $CDCl_3$ revealed an approximately 2:1 ratio of **19** and **10.**

***(1R*,5R,6R,7S)*-8-Spiro-2'-(1',3'-dioxolane)-5-cyano-1,7-dimethyl-3-oxabicyclo[4.4.0]-decan-4-one (11a)** and ***(1R*,5R,6R,7S)*-4,8-bis[spiro-2'-(1',3'-dioxolane)]-5-cyano-1,7-dimethyl-3-oxabicyclo[4.4.0]decane (11b):** A suspension of **7** (1.12 g, 5.05 mmol), ethylene glycol (1.49 g, 24 mmol), and pyridinium *p*-toluenesulfonate (63 mg, 0.25 mmol) in benzene (ca. 150 mL) was allowed to reflux under a Dean-Stark trap overnight. The reaction mixture was diluted with EtOAc, and the solution was washed twice with water, then shaken with brine. It was dried over $MgSO_4$ and evaporated to give a white solid. Flash chromatography (60% EtOAc/ petroleum ether) provided **11b** (0.22 g, 0.71 mmol, 14% yield) as plates, mp 130-135 °C, and, after recrystallisation from hot EtOH, **11a** (0.91 g, 3.45 mmol, 68% yield) as very fine needles, mp 160-161 °C. **11a:** ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.41 (d, 11.6 Hz, 1H), 3.95 (m, 5H), 3.77 (d, 5.3 Hz, 1H), 2.15 (ddd, 9.0 Hz, 5.0 Hz, 1.0 Hz, 1H), 1.93 (dq, J_d= 9.0 Hz, J_q= 6.8 Hz, 1H), 1.6-1.8 (m, 3H), 1.49 (m, 1H), 1.22 (s, 3H), 1.11 (d, 6.7 Hz, 3H). ^{13}C NMR + APT (100 MHz, $CDCl_3$): δ 164.0 (?), 116.9 (e), 109.0 (e), 75.2 (e), 65.1 (e), 64.9 (e), 48.7 (o), 41.1 (o), 36.4 (o), 32.6 (e, quat), 31.0 (e), 29.5 (e), 25.5 (o), 13.1 (o). IR (Nujol): 2250 (v. weak), 1722, 1194, 1102, 1060, 1041 cm^{-1}. Anal.: Calc. for $C_{14}H_{19}NO_4$: C 63.38, H 7.22, N 5.28; found: C 63.40, H 7.24, N 5.19. **11b:** ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.05-4.25 (m, 4H), 3.9-4.0 (m, 5H), 3.63 (d, 8.9 Hz, 1H), 3.23 (d, 8.9 Hz, 1H), 2.14 (q, 7.5 Hz, 1H), 2.08 (m, partly obscured, 1H), 2.02 (d, 12.0 Hz, 1H), 1.92 (dt, J_d= 4.2 Hz, J_t= 3.6 Hz, 1H), 1.50 (borad d, 13.6 Hz, 1H), 1.18 (d + m, J_d= 7.5 Hz, 4H), 1.00 (s, 3H). ^{13}C NMR + APT (100 MHz, $CDCl_3$): δ 119.3 (e), 117.2 (e), 109.9 (e), 73.2 (e), 65.7 (e), 64.5 (e), 63.9 (e), 47.8 (o), 39.2 (o), 37.8 (o), 31.7 (e, quat), 28.2 (e), 27.1 (e), 23.6 (o), 18.4 (o). A minor diastereomer could also be seen in the ^{13}C NMR spectrum of **11b**; this is probably the epimer at C5 or C7. IR (Nujol): 1216, 1194, 1149, 1135, 1116, 1096, 1078, 1022, 948 cm^{-1}. Anal.: Calc. for $C_{16}H_{23}NO_5$: C 62.12, H 7.49, N 4.53. Found: C 62.20, H 7.55, N 4.43. The stereochemistry of **11a** at C5 is not established with certainty.

***(1R*,5RS,6R,7S)*-8,8-Bis(benzyloxy)-5-cyano-1,7-dimethyl-3-oxabicyclo[4.4.0]decan-4-one (12):** A solution of **7** (1.70 g, 7.69 mmol), benzyl alcohol (4.2 mL, 41 mmol), and pyridinium *p*-toluenesulfonate (98 mg, 0.39 mmol) in benzene (ca. 50 mL) was brought to reflux under a Dean-Stark trap which contained some 4 Å molecular sieves. After 1 d, another portion of benzyl alcohol (4.2 mL, 41 mmol)

was added. After 2 d more, the reaction mixture was allowed to cool to room temperature. It was diluted with CH_2Cl_2 and shaken with water, and the aqueous layer was back-extracted with CH_2Cl_2. The combined organic layers were shaken with brine, dried over $MgSO_4$, and evaporated. Flash chromatography (15%, then 20%, then 60% EtOAc/ petroleum ether) afforded clean **7**, which was recrystallised from hot EtOH (140 mg, 0.63 mmol, 8% recovery), but no separation of product and benzyl alcohol was achieved. This mixture was subjected to Kugelrohr distillation to remove excess alcohol. The undistilled residue was rechromatographed (CH_2Cl_2) to afford **12** (975 mg, 2.32 mmol, 30% yield) as a viscous, colourless oil consisting of a 2:1 mixture of diastereomers. Resonances due only to the minor diastereomer are presented in {braces}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.2-7.4 (m), altogether 10H. δ 5.25 (m), 4.71 (d, 11.5 Hz), {4.66 (d, 11.5 Hz)}, 4.53 (d, 11.5 Hz), {4.50 (d, 11.5 Hz)}, altogether 4H. δ {4.36 (dd, 9.8 Hz, 3.2 Hz)}, 4.25 (dd, 9.8 Hz, 3.3 Hz), 3.73 (d, 4.7 Hz), 3.71 (dd, 9.8 Hz, 1.4 Hz), {3.65 (d, ~5.1 Hz)}, {3.63 (dd, ~11 Hz, 1.6 Hz)}, altogether 3H. δ 2.37 (approx. d quintet, J_d≈ 1.7 Hz, J_q≈6.6 Hz), {2.14 (approx. d quintet, J_d≈ 1.5 Hz, J_q≈7.1 Hz)}, altogether 1H. δ {2.07 (m)}, 1.9-2.0 (m), 1.5-1.8 (m), altogether 5H. δ {1.05 (d, 7.1 Hz)}, 0.96 (d, 6.9 Hz), {0.84 (s)}, 0.80 (s), altogether 6H. ^{13}C NMR + APT (100 MHz, $CDCl_3$): Major diastereomer: δ 166.5 (e), 138.7 (e), 134.2 (e), 115.9 (e), 100.1 (e), 71.2 (e), 68.8 (e), 63.6 (e), 50.1 (o), 39.6 (o), 38.7 (o), 35.0 (e), 32.6 (e), 25.7 (e), 20.2 (o), 17.3 (o). Minor diastereomer: δ 166.0 (e), 138.6 (e), 134.2 (e), 116.3 (e), 100.3 (e), 71.5 (e), 68.7 (e), 63.6 (e), 49.5 (o), 39.3 (o), 39.0 (o), 35.6 (e), 33.0 (e), 25.5 (e), 19.9 (o), 16.2 (o). Unassigned resonances: δ 129.0 (o), 128.9 (o), 128.6 (o), 128.3 (o), 127.6 (o), 127.5 (o), 127.4 (o), 127.3 (o). IR (neat): 3032, 2962, 2873, 2248, 1745, 1496, 1466, 1378, 1350, 1309, 1260, 1214, 1173, 1102, 1047, 994, 926, 737, 698 cm^{-1}. HRMS: Calc. for $C_{26}H_{29}NO_4$: 419.2096; found: 419.2116. The diastereomers were assigned as epimers at C5, as they gave a single diastereomer in the next reaction.

(*1R*,5S,6R,7R*)- and (*1R*,5R,6R,7S*)-5-Cyano-8-methylene-1,7-dimethyl-3-oxabicyclo-[4.4.0]decan-4-one (13): *n*-Butyllithium (1.8 mL of 2.5 *M* solution in hexane, 4.5 mmol) was added to a suspension of triphenylmethylphosphonium bromide (1.58 g, 4.41 mmol) in dry THF (40 mL) under Ar at 0 °C. After 40 min, the bright orange solution (some solid still present) was cooled to -78 °C, and **7** (443 mg, 2.00 mmol) was added. After 35 min, the bright yellow suspension was allowed to warm to room temperature. A white precipitate formed. After ca. 1 h, the reaction mixture was quenched with a small amount of 1 *N* HCl, whereupon the yellow colour disappeared, and much of the precipitate redissolved. The solvent was evaporated. The residue was diluted with ether and water, and the aqueous layer was brought to pH 6 with more 1 *N* HCl. The mixture was shaken, and the organic layer was shaken with water and brine, dried over $MgSO_4$, and evaporated to give an orange oil. This was purified by flash chromatography (20%, then 25%, then 30% EtOAc/ petroleum ether) to afford **13** (219 mg, 1.00 mmol, 50% yield) as a colourless oil consisting of a 5.5:1 mixture of diastereomers. Resonances due only to the minor diastereomer are presented in {braces}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.92 (m), altogether 2H. δ {4.49 (d, 12.1 Hz),} 4.08 (d, 11.7 Hz), {4.00 (d, 12.2 Hz)}, 3.98 (d, 11.7 Hz), altogether 2H. δ {3.79 (d, 5.7 Hz)}, 3.48 (d, 9.2 Hz), altogether 1H. 2.4-2.6 (m), 2.20 (dt, J_d= 15.2 Hz, J_t= 6.1 Hz), 2.01 (dd, 9.1 Hz, 4.5 Hz), {1.87 (ddd, 13.7 Hz, 11.5 Hz, 8.1 Hz)}, 1.5-1.7 (m), {1.39 (m)}, altogether 6H. δ 1.32 (d, 7.1 Hz), 1.18 (s), {1.14 (d, 6.5 Hz}, {1.09 (s)}, altogether 6H. ^{13}C NMR + APT (100 MHz, $CDCl_3$): Major diastereomer: δ 164.2 (e), 145.9 (e, quat), 112.5 (e), 109.3 (e, quat), 76.3 (e), 49.5 (o), 41.1 (o), 37.0 (o), 33.0 (e, quat), 31.0 (e), 27.0 (e), 25.1 (o), 19.7 (o). Minor diastereomer: δ 146.9 (e, quat), 116.3 (e), 113.6 (e, quat), 76.9 (e), 48.1 (o), 35.4 (o), 35.2 (o), 34.1 (e, quat), 28.7 (e), 26.9 (o), 15.6 (o), two resonances obscured. IR (neat): 3072 (v. weak), 2968, 2934, 2252 (weak), 1747, 1646 (weak), 1470, 1382, 1242, 1204, 1170, 1057, 900 cm^{-1}. HRMS: Calc. for $C_{13}H_{17}NO_2$: 219.1259; found: 219.1256. The stereochemistry of the major isomer is assigned to be opposite

to that of **7** at C7 because of the large H5-H6 coupling constant, which suggests an axial-axial interaction. The minor diastereomer is assigned as the epimer at C7 and perhaps also at C5.

(*1R*,5S,6R,7S,8R*)-8-Hydroxy-5-cyano-1,7-dimethyl-3-oxabicyclo[4.4.0]decan-4-one (14): Sodium hydride (93 mg of 60% suspension in mineral oil, 2.33 mmol) was added to a solution of **7** (442 mg, 2.00 mmol) in dry THF (40 mL) under Ar. Gas evolved, and most of the NaH dissolved. When the evolution of gas had ceased, the solution was cooled to -78 °C, and L-Selectride© (2.2 mL of 1 *M* solution in THF, 2.2 mmol) was added. The solution was allowed to warm to room temperature. A precipitate formed. The reaction mixture was quenched by the addition of 1 *N* HCl (5 mL), causing some evolution of gas, and the solution was evaporated. The residue was diluted with CH_2Cl_2, water, and brine, and the mixture was shaken. The aqueous layer was back-extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and evaporated. Flash chromatography was conducted twice (first time, 3.5%, then 4% EtOH/ CH_2Cl_2; second time, 65%, then 70% EtOAc/ petroleum ether) but failed to give pure product. The product was dissolved in CH_2Cl_2 and extracted first with sat. aq. $NaHCO_3$ and then with sat. aq. Na_2CO_3. The aqueous layers were acidifed with conc. HCl and extracted with two portions of CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and evaporated to give **14** (303 mg, 1.36 mmol, 68% yield) as a glassy oil of ca. 90% purity, which slowly solidified. This material was characterised as well as possible, then carried on to the next step. ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.55 (d, 11.4 Hz, 1H; 2β), 3.91 (dd, 11.5 Hz, 1.9 Hz, 1H; 2α), 3.87 (m, 1H; 8), 3.48 (d, 3.1 Hz, 1H; 5), 2.23 (ddd, 11.6 Hz, ~2.5 Hz, ~2.5 Hz, 1H; 9), 1.92 (dt, J_t= 14.0 Hz, J_d= 4.6 Hz, 1H; 10α), 1.73 (dq, J_d= 14.4 Hz, J_q= 4.0 Hz, 1H; 9α), overlaps with 1.6-1.7 (m, 2H; 7, OH), which overlaps with 1.55 (ddt, J_t= 14.1 Hz, J_d≈ 3.0 Hz, J_d≈ 4.2 Hz, 1H; 9β), 1.35 (dt, J_d= 14.4 Hz, J_t= 3.9 Hz, 1H; 10β), 1.22 (s, 3H; 1-Me), 1.18 (d, 6.7 Hz, 3H; 7-Me). ^{13}C NMR + APT (100 MHz, $CDCl_3$): δ 164.0 (e), 117.3 (e), 74.5 (e), 69.4 (o), 45.2 (o), 38.2 (o), 35.5 (o), 32.9 (e, quat), 28.5 (e), 28.4 (e), 25.9 (o), 16.2 (o). IR (neat): 3516, 2964, 2881, 2252, 1736 (fine structure), 1462, 1403, 1384, 1264, 1245, 1198, 1063, 1036, 999 cm^{-1}. HRMS: Calc. for $C_{12}H_{17}NO_3$: 223.1208; found: 223.1209.

(*1R*,7S*)-8-Spiro-2'-(1',3'-dioxolane)-5-hydroxy-1,7-dimethyl-3-oxabicyclo[4.4.0]dec-5-en-4-one (15) and methyl (*1R*,5S,6S,7S*)-4-spiro-2'-(1',3'-dioxolane)-7-hydroxy-1,5-dimethyl-8-oxabicyclo[4.3.0]nonane-7-carboxylate (16a): A suspension of **11a** (808 mg, 3.05 mmol) in dry methanol (40 mL) under Ar was treated with KO-*t*-Bu (397 mg, 3.54 mmol). The solid dissolved completely. The solution was cooled to -78 °C, and 2-(4-methoxybenzenesulfonyl)-3-(4-nitrophenyl)-oxaziridine[7] (2.26 g, 6.72 mmol) was added. The suspension was allowed to warm to room temperature. As it warmed, the oxaziridine slowly dissolved, and the reaction mixture turned dark red. After stirring at room temperature for 2.5 h, the solvent was evaporated on the rotary evaporator. The product was subjected to flash chromatography (40% EtOAc/ petroleum ether) to give an orange solid. The solid was rinsed with four portions of ether to give **15** as a white solid. The ether washes were evaporated and rechromatographed (8% ether/ CH_2Cl_2). A mixture of solid **15** and oil **16a** was obtained. This was again rinsed with ether, and the solid was combined with previously obtained material to give **15** (449 mg, 1.77 mmol, 58% yield) as a white microcrystalline solid, mp 186 °C. The oil containing **16a** was chromatographed once again (10% EtOH/ petroleum ether). Under these conditions, most of the **16a** was converted to another species, which was identified by ^{1}H NMR as the corresponding ethyl ester, **16b.** Therefore the oil was dissolved in MeOH and allowed to stir over a small amount of silica gel overnight. The mixture was filtered and evaporated to give homogeneous **16a** (6 mg, ca. 0.02 mmol, ca. 1% yield) by TLC, but NMR in either $CDCl_3$ or CD_3OD showed ~2.7:1 mixture of **16a** and **15. 15:** ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.70 (s, 1H), 4.08 (d, 10.7 Hz, 1H), 3.9-4.0 (m, 5H), 3.08 (dq, J_q= 7.5 Hz, J_d= 1.7 Hz, 1H), 2.02 (m, 1H), 1.58 (m, 2H), 1.46 (m, 1H), 1.33 (s, 3H), 1.17 (d, 7.5 Hz, 3H). ^{13}C NMR + APT (100 MHz, $CDCl_3$): δ 164.1 (e), 134.6 (e), 134.4 (e), 109.9

(e), 79.0 (e), 64.7 (e), 64.2 (e), 36.8 (o), 33.4 (e, quat), 31.4 (e), 25.4 (e), 24.7 (o), 16.4 (o). IR (Nujol): 3405, 1698, 1661 (shoulder), 1263, 1231, 1197, 1136, 1102, 788 cm^{-1}. Anal.: Calc. for $C_{13}H_{18}O_5$: C 61.41, H 7.14; found: C 61.51, H 7.15. **16a** (as 2.7:1 mixture with **15**): ^1H NMR (400 MHz, $CDCl_3$): δ 4.00 (m, 5H?), 3.79 (s, 3H), 3.68 (d, 8.6 Hz, 1H), 3.57 (d, 8.6 Hz, 1H), 2.43 (s, 1H), 2.18 (~tq, J_q= 7.5 Hz, 1H), 2.02 (m, 1H), 1.90 (apparent dt, 1H), 1.5-1.6 (m, 2H?), 1.20 (s, 3H), 1.15 (d, 7.5 Hz, 3H). ^{13}C NMR + APT (100 MHz, $CDCl_3$): δ 172.0 (e), 110.6 (e), 104.3 (e), 78.5 (e), 64.4 (e), 64.3 (e), 57.1 (o), 52.8 (o), 39.1 (e, quat), 35.0 (o), 31.7 (e), 27.4 (e), 24.9 (o), 18.1 (o).

Methyl (*1R*,4R,5S,6S*)-1-benzyloxy-4,6-dimethyl-2-oxabicyclo[2.2.2]octane-5-glyoxylate (17): A solution of **12** (970 mg, 2.32 mmol) in dry MeOH (ca. 100 mL) under Ar was treated with KO-*t*-Bu (314 mg, 2.80 mmol). The solution was cooled to -78 °C, and 2-(4-methoxybenzenesulfonyl)-3-(4-nitrophenyl)oxaziridine[7] (1.72 g, 5.11 mmol) was added. The mixture was allowed to warm to room temperature. As it warmed, the oxaziridine slowly dissolved, and the reaction mixture turned dark red. After stirring at room temperature for 1 h, the solvent was evaporated on the rotary evaporator. The dark red residue was twice subjected to flash chromatography (15% EtOAc/ petroleum ether) to afford **17** (436 mg, 1.31 mmol, 57% yield) as a light yellow oil. ^1H NMR (400 MHz, $CDCl_3$): δ 7.2-7.35 (m, 5H), 4.75 (d, 11.5 Hz, 1H), 4.52 (d, 11.5 Hz, 1H), 4.12 (dd, 9.2 Hz, 2.6 Hz, 1H), 3.88 (s, 3H), 3.58 (dd, 9.2 Hz, 1.6 Hz, 1H), 3.27 (dd, 6.5 Hz, 1.5 Hz, 1H), 2.62 (quintet, 6.1 Hz, 1H), 1.95 (m, 2H), 1.73 (m, 2H), 1.04 (d, 7.0 Hz, 3H), 0.81 (s, 3H). ^{13}C NMR + APT (100 MHz, $CDCl_3$): δ 195.8 (e), 162.7 (e), 138.7 (e), 128.3 (o), 127.5 (o), 127.3 (o), 100.0 (e), 71.6 (e), 63.6 (e), 55.9 (o), 53.2 (o), 36.2 (o), 34.9 (e), 34.2 (e, quat), 25.9 (e), 19.9 (o), 17.0 (o). The structure and stereochemistry of **17** were established and confirmed by COSY and NOESY experiments. IR (neat): 2956, 2872, 1730, 1465, 1350, 1261, 1172, 1104, 1074, 1039 cm^{-1}. HRMS: Calc. for $C_{19}H_{24}O_5$: 332.1624; found: 332.1623.

(*1R*,7S*)-5-Hydroxy-8-methylene-1,7-dimethyl-3-oxabicyclo[4.4.0]dec-5-en-4-one (18): A solution of **13** (217 mg, 0.99 mmol) in dry methanol (ca. 30 mL) under argon was treated with KO-*t*-Bu (135 mg, 1.20 mmol). The solution was cooled to -78 °C, and 2-(4-methoxybenzenesulfonyl)-3-(4-nitrophenyl)-oxaziridine[7] (774 mg, 2.30 mmol) was added. The mixture was allowed to warm to room temperature. As it warmed, the oxaziridine slowly dissolved, and the reaction mixture turned dark red. After stirring at room temperature for 1 h, the solvent was evaporated on the rotary evaporator. The dark red residue was twice subjected to flash chromatography (first time, 15% EtOAc/ petroleum ether; second time, 12% EtOAc/ petroleum ether), and the product that was obtained was recrystallised from slowly evaporating ether/ heptane to give **18** (101 mg, 0.48 mmol, 49% yield) as colourless prisms, mp 107 °C, admixed with some needles. ^1H NMR (400 MHz, $CDCl_3$): δ 5.62 (s, 1H), 4.79 (s, 1H), 4.75 (t, 1.7 Hz, 1H), 3.98 (*AB*, 2H), 3.69 (q, 7.4 Hz, 1H), 2.51 (tm, 14.0 Hz, 1H), 2.20 (dt, J_d= 14.1 Hz, J_t= 3.2 Hz, 1H), 1.60 (dt, J_d= 12.7 Hz, J_t= 3.6 Hz, 1H), 1.38 (s, 3H), 1.28 (dt, partly obscured, J_t≈ 13.3 Hz, J_d= 3.9 Hz, 1H), 1.27 (d, 7.5 Hz, 3H). ^{13}C NMR + APT (100 MHz, $CDCl_3$): δ 164.3 (e, quat), 148.9 (e, quat), 135.2 (e, quat), 133.1 (e, quat), 109.6 (e), 78.9 (e), 36.5 (o), 35.3 (e), 34.1 (e, quat), 25.8 (e), 24.0 (o), 21.8 (o). IR (Nujol): 3388 (sharp), 1698, 1358, 1255, 1226, 1184, 1136, 907 cm^{-1}. Anal.: Calc. for $C_{12}H_{16}O_3$: C 69.21, H 7.74; found: C 69.14, H 7.76.

(*1R*,7S,8R*)-5,8-Dihydroxy-1,7-dimethyl-3-oxabicyclo[4.4.0]dec-5-en-4-one (19): A solution of **14** (301 mg, 1.35 mmol, ca. 90% pure) in dry methanol (ca. 50 mL) under argon was treated with KO-*t*-Bu (177 mg, 1.58 mmol). The solution was cooled to -78 °C, and 2-(4-methoxybenzenesulfonyl)-3-(4-nitrophenyl)oxaziridine[7] (1.06 g, 3.15 mmol) was added. The mixture was allowed to warm to room temperature. As it warmed, the oxaziridine slowly dissolved, and the reaction mixture turned dark red. After 45 minutes, TLC showed the presence of a single ammonium molybdate-active spot; this spot was not UV-

active. The solvent was evaporated on the rotary evaporator. The dark red residue was twice subjected to flash chromatography (first time, 55%, then 60% EtOAc,/ petroleum ether; second time, 3.5%, then 4.0% EtOH/ CH_2Cl_2), and the solid which was obtained was recrystallised twice from slowly evaporating CH_2Cl_2/ heptane to give **19** (102 mg, 0.48 mmol, ca. 40% yield) as light yellow needles, mp 193-194 °C, that were only slightly soluble in $CDCl_3$. ^1H NMR (400 MHz, $CDCl_3$): δ 5.64 (s, 1H), 3.98 (*AB*, 10.6 Hz, 2H), 3.79 (ddd, 10.2 Hz, 6.0 Hz, 4.2 Hz, 1H), 3.35 (d-quintet, $J_q \approx$ 6.8 Hz, $J_d \approx$ 0.9 Hz, 1H), 1.82 (ddt, $J_t \approx$ 13.3 Hz, $J_d \approx$ 11.9 Hz, $J_d \approx$ 3.4 Hz, 1H), 1.71 (ddq, $J_d \approx$ 13.2 Hz, $J_q \approx$ 3.8 Hz, $J_d \approx$ 1.1 Hz, 1H), 1.56 (dt, partly obscured by H_2O, $J_d \approx$ 13.1 Hz, $J_t \approx$ 3.5 Hz, 1H), 1.33 (s, 3H), 1.27 (dt, $J_t \approx$ 13.5 Hz, $J_d \approx$ 3.9 Hz, 1H), 1.24 (s, 1H), 1.14 (d, 7.4 Hz, 3H). ^1H NMR (400 MHz, CD_3OD): δ 3.97 (*AB*, 10.6 Hz, 2H), 3.69 (ddd, 10.0 Hz, 5.9 Hz, 4.0 Hz, 1H), 3.35 (d-quintet, $J_q \approx$ 7.0 Hz, $J_d \approx$ 0.7 Hz, 1H), 1.82 (ddt, $J_t \approx$ 13.1 Hz, $J_d \approx$ 11.9 Hz, $J_d \approx$ 3.4 Hz, 1H), 1.64 (ddq, $J_d \approx$ 13.0 Hz, $J_q \approx$ 3.7 Hz, $J_d \approx$ 1.1 Hz, 1H), 1.57 (dt, $J_d \approx$ 13.5 Hz, $J_t \approx$ 3.4 Hz, 1H), 1.30 (s+dt, $J_t \approx$ 13.5 Hz, $J_d \approx$ 3.8 Hz, 4H), 1.10 (d, 7.3 Hz, 3H). ^{13}C NMR + APT (100 MHz, $CDCl_3$): δ 164.1, 134.6, 134.4 (e), 79.1 (e), 71.0 (o), 33.7 (e, quat), 33.5 (o), 32.8 (e), 24.6 (o), 24.2 (e), 12.3 (o). ^{13}C NMR + APT (100 MHz, CD_3OD): δ 165.3 (e), 137.5 (e), 136.6 (e), 80.0 (e), 72.0 (o), 34.8 (e, quat), 34.8 (o), 33.8 (e), 24.9 (o+e, 2C), 13.0 (o). IR (Nujol): 3452 (sharp), 3257 (broad), 1694, 1407, 1250, 1226, 1185, 1121, 1065, 1007, 785 cm^{-1}. Anal.: Calc. for $C_{11}H_{16}O_4$: C 62.25, H 7.60; found: C 62.36, H 7.57.

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13. (a) We discovered later that the main contaminant was 4-hydroxymethyl-2,4-dimethyl-2-cyclohexen-1-o1. The diol is diacylated in the next step, and the product is easily separated from the desired ketoester by chromatography. It was probably obtained because some hydrolysis of the labile enol ether intermediate, followed by reduction with unquenched $LiAlH_4$, occurred during Fieser work-up. The proportion of diol varied from run to run and increased with larger scales. We have not sought yet to redevelop conditions for this work-up, but we recommend that excess $LiAlH_4$ be quenched with EtOAc before Fieser work-up is conducted. (b) We later found that only a small amount of 1 *N* HCl and stirring for 0.5 h is actually necessary.
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