Toward a Total Synthesis of Macrocyclic Jatrophane Diterpenes – Concise Route to a Highly Functionalized Cyclopentane Key Intermediate

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Dedicated to Professor *Rolf Huisgen* on the occasion of his 85th birthday

A total synthesis of the biologically potent jatrophane diterpenes pepluanin A (**1**) and euphosalicin A (**2**) is being aimed at. *En route* to these targets, a concise synthesis of the nonracemic cyclopentane building block **74** was developed. Key steps were a *Claisen – Eschenmoser* rearrangement of the enantiomerically enriched allylic alcohol **14** to amide **34** (*Scheme 7*), a hydroxy-lactonization of **40** to **43** (*Scheme 9*), followed by *trans*-lactonization to **72**, which was subjected to a *Davis* hydroxylation to **69** (*Scheme 17*). Eventually, compound **69** was converted into the enol triflate **74**. This material should prove suitable for an annulation of the macrocyclic ring characteristic of the desired jatrophanes **1** and **2**. Less-successful approaches are also discussed due to their intrinsically valuable information content.

Introduction. – Any kind of cancer chemotherapy is threatened by intrinsic or acquired multidrug resistance (MDR[1]). Nearly 50% of human cancers are either completely resistant to chemotherapy or respond only transiently, whereafter they are no longer affected by commonly used anticancer drugs. The phenomenon of MDR was first discovered by *Shapiro* and *Ling*, who observed that human tumors treated sequentially with different chemotherapeutics became resistant to further chemotherapy [1]. Thus, certain kinds of cancer cannot be treated successfully by means of chemotherapy. A primary mechanism of MDR is attributed to the overexpression of P-glycoprotein (P-gp) in the plasma membrane or in resistant cells, where the P-gp acts as an energy-dependent efflux pump, reducing intracellular accumulation of anticancer drugs [2]. A number of drugs such as calcium channel blockers, calmodulin inhibitors, and certain indole alkaloids are known to reverse MDR by competing with anticancer drugs for binding to P-gp. However, they have not been proven clinically useful yet. For example, *Verapamil*®, the most extensively studied MDR-reversing agent, induces cardiovascular toxicity at the concentration that is needed to reverse MDR [3]. Clearly, there is a need for new classes of MDR-reversing agents with less toxicity to the host.

In a search for MDR-reversing compounds from natural sources, the secondary metabolites of *Euphorbia* species, perennial herbs distributed throughout Central and South-East Europe, were investigated [4]. The Euphorbiaceae (spurge) family is known to produce various highly functionalized, structurally unique macrocyclic diterpenes. The MDR-reversing effect of lipophilic extracts of *Euphorbia esula* L., *E.*

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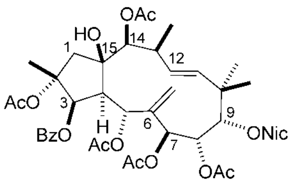
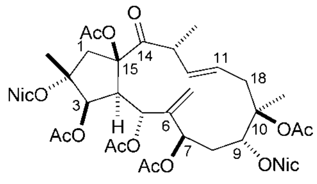
[1]) For abbreviations, see *Exper. Part.*

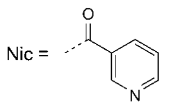
peplus L., *E. salicifolia*, and *E. serrulata* were tested on mouse lymphoma cells. From the active extracts, a series of structurally related compounds with significant P-gp inhibitory activities were isolated, including pepluanin A (**1**) and euphosalicin (**2**).



Pepluanin A (**1**)

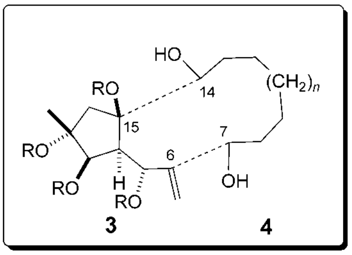


Euphosalicin (**2**)



Bz = benzoyl

Ac = acetyl

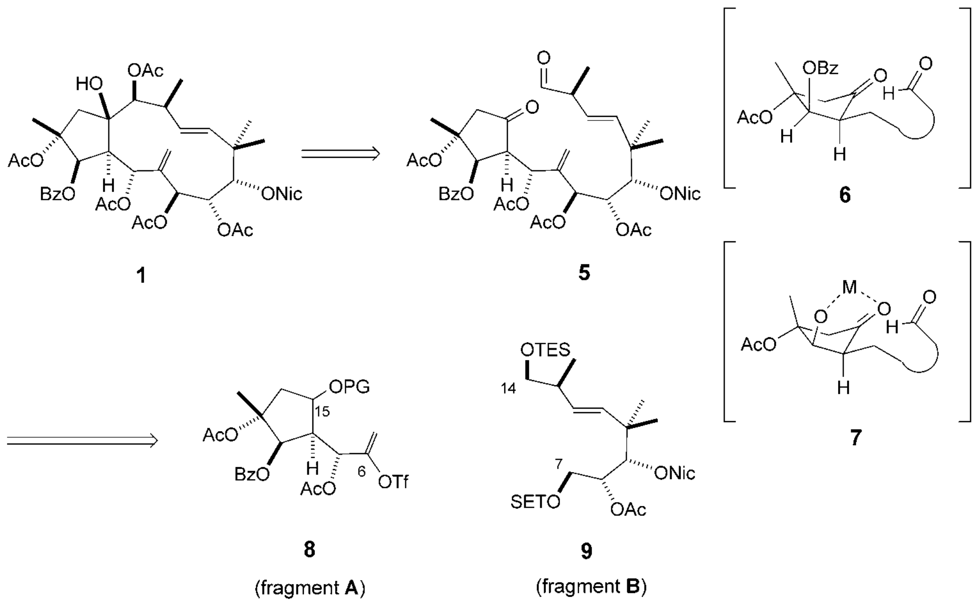


3 **4**

Results and Discussion. – To gain deeper insight into structure–activity relationship (SAR), we [5] and others [6] thought about a general synthetic access to pepluanin A (**1**) and euphosalicin (**2**), as well as other structurally related jatrophane natural products. Structural analysis of **1** and **2** revealed that the differences in the oxygenation patterns and carbon skeletons lie primarily in the C(7–14) segment of the larger ring. Therefore, we envisaged a C(15–6) segment (**3**) common to both targets, which should then be coupled to a tailor-made C(7–14) segment (**4**).

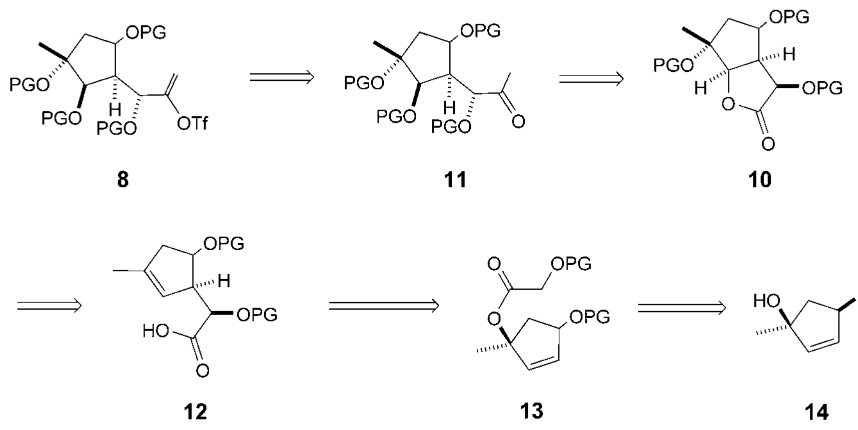
A retrosynthetic analysis of **1** suggested that formation of the bonds C(14)–C(15) and C(6)–C(7) at a late stage might be achieved *via McMurry* [7] and *Nozaki–Hiyama–Kishi* (NHK) type [8] couplings, respectively (*Scheme 1*). The stereochemical implications of a *McMurry* type coupling for the ring closure of keto aldehyde **5** were then considered. The approach of the aldehyde moiety from the α-side of the ring should be favored for steric reasons, as illustrated in **6**, affording a diol with the desired relative configuration. If this expectation should not be borne out experimentally, recourse to the free 3-OH group would be expected to undergo the *McMurry* coupling from the desired α-side (see **7**) [7]. The next disconnection of C(6)–C(7) leads back to vinyl triflate **8** and the aldehyde segment **9**, which represent suitable substrates for a NHK-type coupling. Fragment **A**, the C–(15)–C(6) segment, could, thus, serve as an advanced intermediate coupling partner, and allow synthetic access to several natural products upon coupling with the corresponding C(7)(14) segments, *i.e.*, fragment B.

Scheme 1. *Retrosynthetic Analysis of* **1**. For abbreviations, see *Exper. Part.*



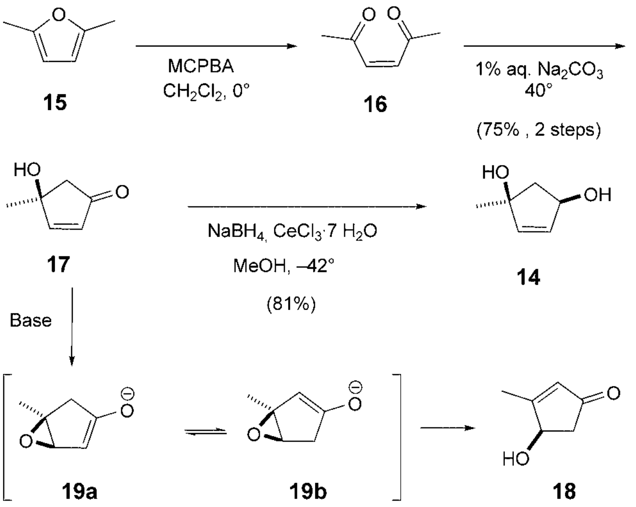
Naturally, the first target of our synthetic study was fragment **A**, the segment common to both proposed syntheses. A straightforward retrosynthetic analysis suggested that vinyl triflate **8** should be available from lactone **10** *via* methyl ketone **11** (*Scheme 2*). In turn, lactone **10** should be accessible from alkene **12** *via* epoxidation of the C=C bond, followed by regioselective opening of the newly formed epoxide. We envisaged acid **12** to be the main product of a *Claisen* type rearrangement of ester **13**, which in turn, should be readily accessible from diol **14**.

Scheme 2. *Retrosynthetic Analysis of* **8**



Diol **14** was prepared in racemic form from 2,5-dimethylfuran (**15**) *via* **16** and the known ketone **17** [9] (*Scheme 3*). It should be noted that prolonged reaction times for the production of **17** lead to formation of the thermodynamically more-stable constitutional isomer **18**, conceivably *via* **19a**,**b** as shown in *Scheme 3*. The desired hydroxy ketone **17** was then subjected to a *Luche* reduction to furnish *cis*-diol **14**. To test the validity of our concept, the following transformations were performed with racemic **14**.

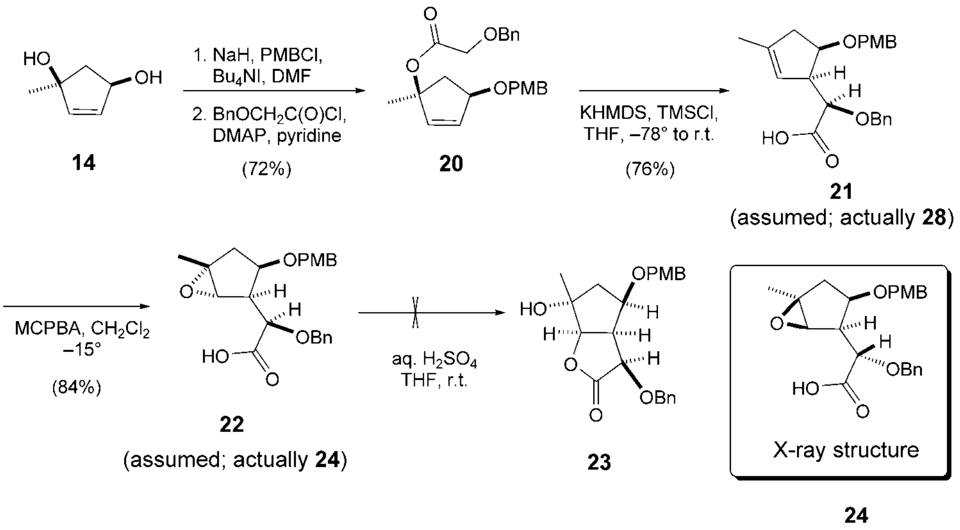
Scheme 3



With racemic diol **14** in hand, the proposed *Ireland–Claisen* rearrangement [10] was investigated. Selective PMB (='*p*-methoxybenzyl') protection of the secondary alcohol function was followed by acetylation of the tertiary alcohol to give **20** (*Scheme 4*). Treatment of the latter with potassium hexamethyldisilazane (KHMDS) and Me_3SiCl (TMSCl) afforded one major product, which, on the basis of NMR studies, was expected to be acid **21**. Epoxidation of the C=C bond in **21** with '*meta*-chloroperbenzoic acid' (MCPBA) gave what we thought to be compound **22**. However, to our disappointment, all attempts at inducing an epoxide-opening lactonization with the neighboring COOH moiety to **23** failed. This result was quite surprising, as literature precedence suggested that this reaction usually proceeds under very mild conditions. However, the reason for this discrepancy soon became clear, when X-ray crystallographic studies were performed on crystals of the putative epoxy acid **21**. Indeed, the structure we had assigned to **22** was inconsistent with the X-ray data, which showed this compound to have structure **24** (*Fig. 1*).

Both the relative configurations of the side chain with the benzyl ether and the epoxide on the ring were wrong in our original assignment. This certainly explained why we were unable to open the epoxide with the COOH moiety! Clearly, the predicted stereochemical outcomes for both the *Ireland–Claisen* rearrangement and the epoxidation had been false.

Scheme 4. *Attempted Preparation of* **21** *and* **22** (see text)



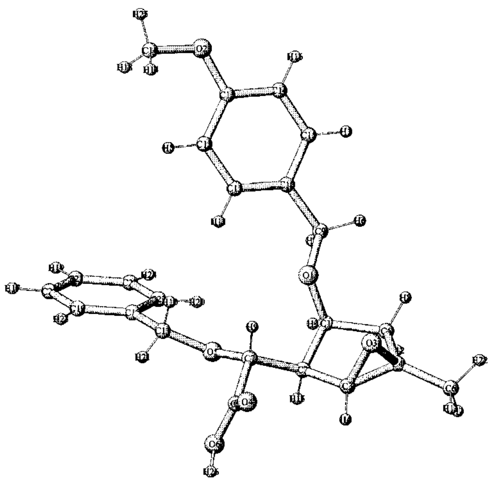
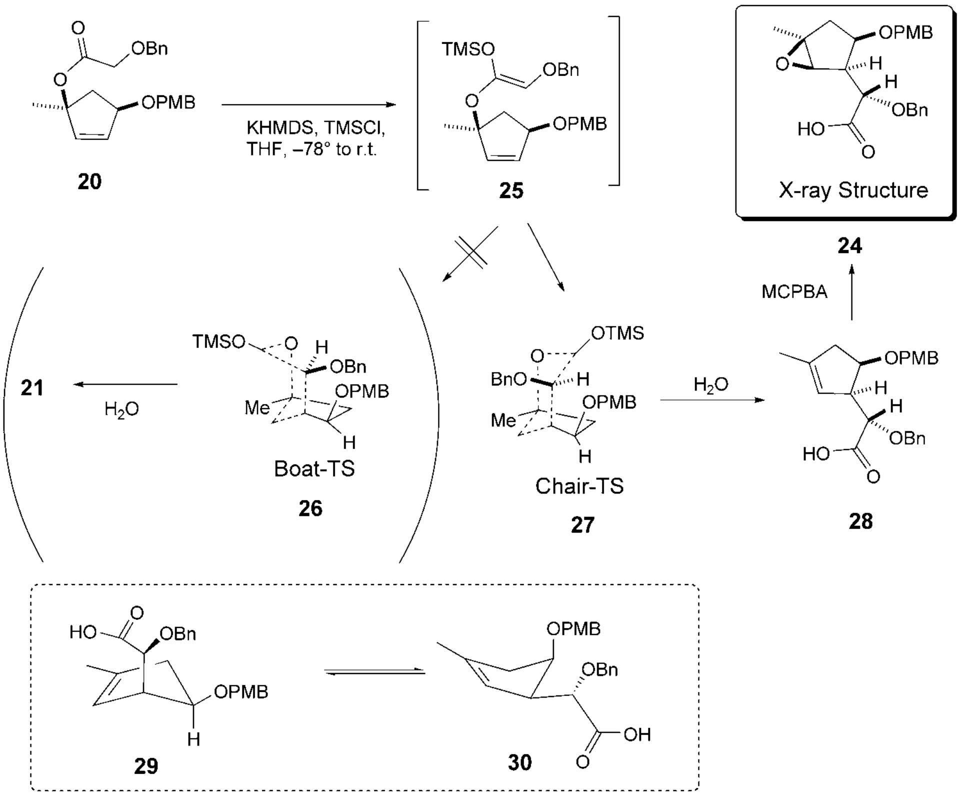


Fig. 1. *X-Ray crystal structure of* **24** (one enantiomer shown)

An analysis of the stereochemical outcome of the *Ireland–Claisen* rearrangement [10] is shown in *Scheme 5*. It is fairly well-established that deprotonation of a BnO-substituted acetate (**20**) under kinetically controlled conditions with KHMDS, followed by quenching of the resulting enolate with TMSCl, should afford the (*Z*)-configured enol ether (**25**). However, the next step of the reaction, the [3,3]-sigmatropic rearrangement, is not so well-established for five-membered rings. In most cases, the rearrangement involves a boat-like transition state similar to **26**, which would then afford the desired product **21**. However, in some cases, namely in our case, the

Scheme 5. *Stereochemical Course of the* Ireland–Claisen *rearrangement of* **20**



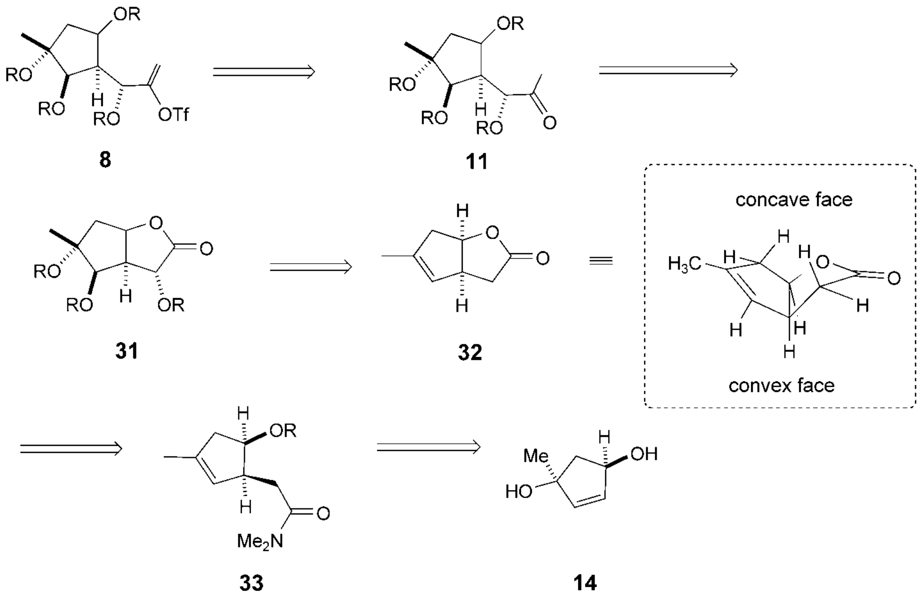
rearrangement can adopt a chair-like transition state similar to **27**, in which the isomer **28** is obtained. Literature precedence [10b,c] has shown that, under certain conditions, the corresponding (*E*)-configured enol ether of **25** can be prepared to access a rearrangement product with the alternate configuration. However, the yields for these reactions tend to be lower, and we decided to abandon this approach.

The, at first sight, contradictory outcome of the epoxidation at **28** is most likely due to a *Henbest* effect exerted by the pseudo-axial COOH function in a conformation such as **29** [11], which is in equilibrium with **30** (*Scheme 5*).

At this point in the study, a new retrosynthetic plan was considered. As in the previous plan, triflate **8** was thought to be accessible from ketone **11** (*Scheme 6*). But this time, access to the ketone would be attempted by opening lactone **31**. We then envisaged that **32** could serve as a template to introduce the challenging oxygenation pattern with the desired configuration in **31**. Thus, we believed that both the epoxidation of the C=C bond and the hydroxylation next to the lactone could be directed to take place from the sterically less-hindered, convex face. Lactone **32** could then be obtained from **33**, the product of an *Eschenmoser–Claisen* rearrangement [12].

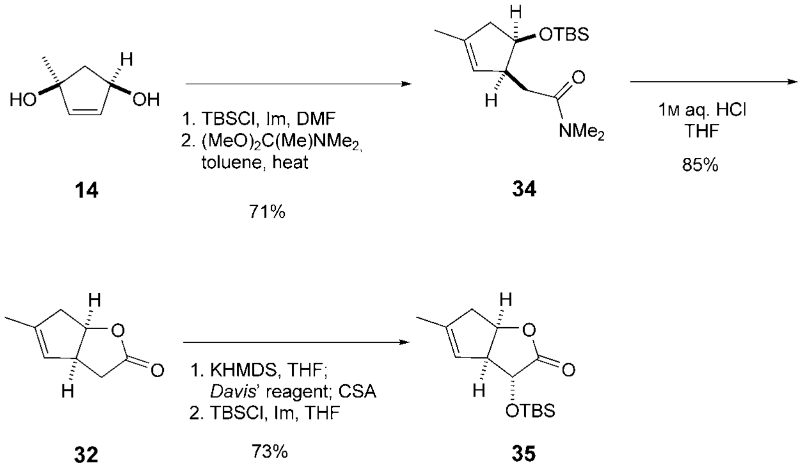
Once again, the first steps of the planned sequence were attempted with racemic diol **14** (Scheme 7). The secondary OH group in **14** was protected as the corresponding

Scheme 6. *Alternative Retrosynthesis of* **8**



tert-butyl(diphenyl)silyl (TBS) ether. Subjection of the resulting material to the *Eschenmoser–Claisen* protocol [12] afforded the amide rearrangement product **34** in good yield. TBS Removal and a subsequent lactonization step were then smoothly effected under acidic aqueous conditions. The resulting material, **32**, was then treated with KHMDS, followed by a solution of the *Davis* oxaziridine [13]. As predicted, the *cis*-fused bicycle underwent hydroxylation completely stereoselectively from the convex

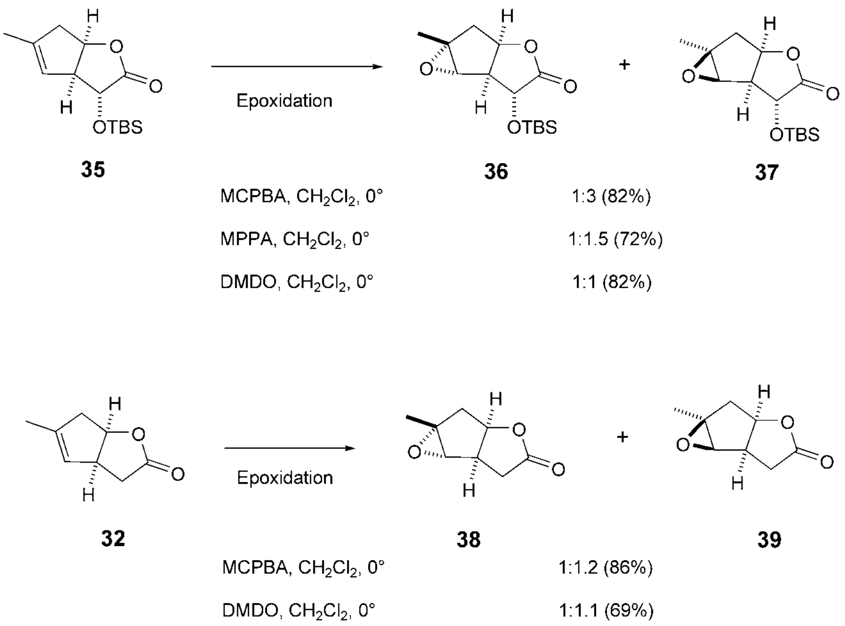
Scheme 7. *Synthesis of the Bicyclic Lactone* **35** (racemic series)



α-face. The newly introduced OH function was then protected as the TBS ether to yield **35**.

The next step in the envisaged strategy foresaw a diastereoselective epoxidation of **35**. However, even under the most-favorable conditions tested, at best, a 1 : 1-mixture of **36**/**37** resulted. The same outcome was observed when **32** served as the starting material to give mixtures of **38**/**39** (*Scheme 8*).

Scheme 8



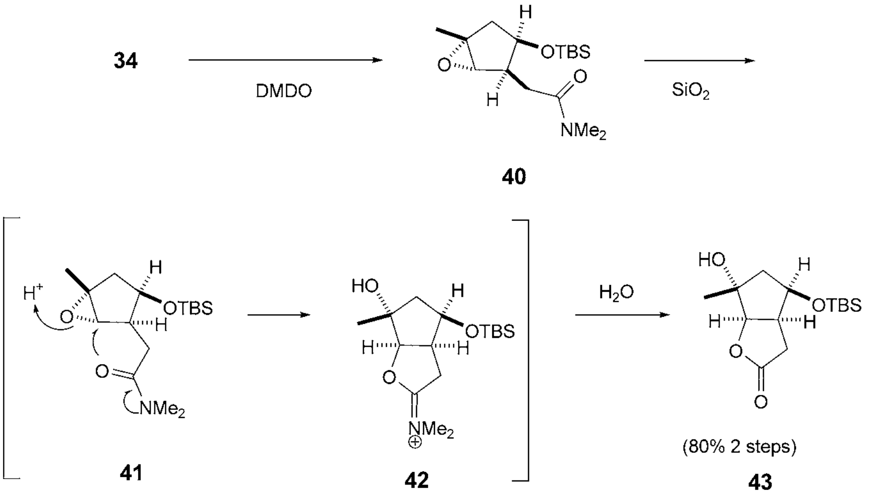
	36 : 37
MCPBA, CH_2Cl_2, 0°	1:3 (82%)
MPPA, CH_2Cl_2, 0°	1:1.5 (72%)
DMDO, CH_2Cl_2, 0°	1:1 (82%)

	38 : 39
MCPBA, CH_2Cl_2, 0°	1:1.2 (86%)
DMDO, CH_2Cl_2, 0°	1:1.1 (69%)

As the epoxidation of the *cis*-fused bicyclic systems did not proceed with the anticipated stereoselectivity, we investigated other precursors as substrates for this key epoxidation step. Gratifyingly, treatment of the *Eschenmoser–Claisen* rearrangement product **34** with *in situ* generated dimethyldioxirane (DMDO) afforded exclusively the desired epoxide **40** (*Scheme 9*). In this case, both the silyl ether and amide side chain moieties on the β-face of **34** were sufficient to direct the attack of the peracid to the α-face. With the epoxide and amide moieties on opposing faces of the ring in **40**, the system was perfectly set up for an intramolecular epoxide-opening lactonization. Indeed, simple flash chromatography of crude **40** produced, *via* **41** and **42**, lactone **43** in 80% overall yield from **34** (*Scheme 9*).

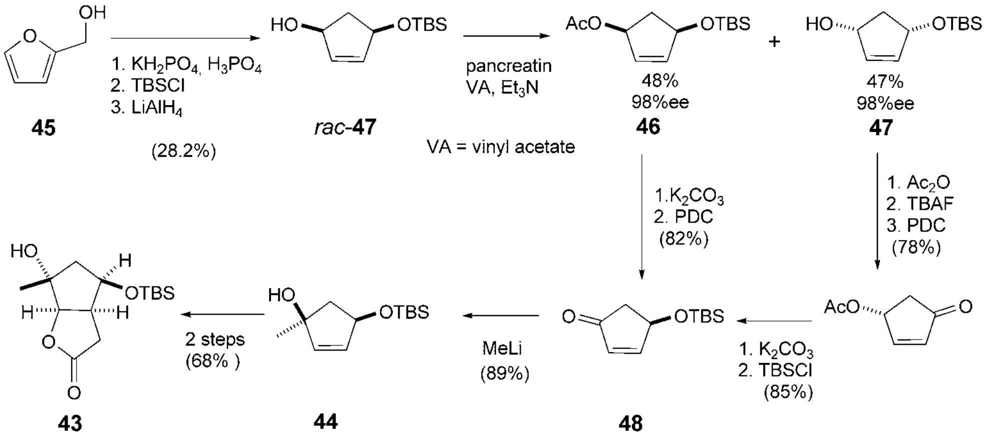
In concurrent studies, ample quantities of enantiomerically enriched starting materials had been prepared. Since all attempts at resolving diol **14** or its derivatives failed in our hands, an alternative approach to prepare enantiomerically enriched **44** was developed (*Scheme 10*). Employing a sequence reported by *Curran* and co-workers [14], commercially available furfuryl alcohol (**45**) was converted in four steps to a separable mixture of acetate **46** (13%, 98% ee) and alcohol **47** (13%, 98% ee). By well-established chemistry [15], compounds **46** and **47** were then converted to a

Scheme 9. *Synthesis of Lactone* **43** (racemic series)



common intermediate, ketone **48** [16], in two and five steps, respectively[2]. Finally, treatment of **48** with MeLi yielded the desired tertiary alcohol **44** [17] in good yield. This enantiomerically enriched material was then carried through the next two newly developed steps to give lactone **43** (98% ee) in good yield.

Scheme 10. *Preparation of Enantiomerically Enriched* **44**



The next challenge in our synthesis was the introduction of an OH substituent α to the lactone function with the desired (*R*)-configuration. To utilize the *convex/concave* handle inherent to *cis*-fused bicycles, it would be necessary to first migrate the lactone function in **43** from the oxygenated 2-position on the ring to the oxygenated 5-position

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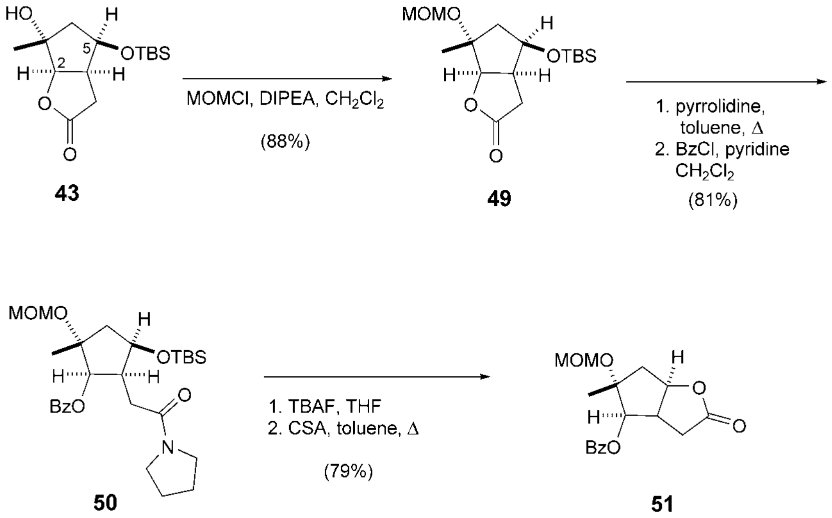
[2] All spectra obtained for intermediates **46**–**48** matched those previously reported in the literature [14–17].

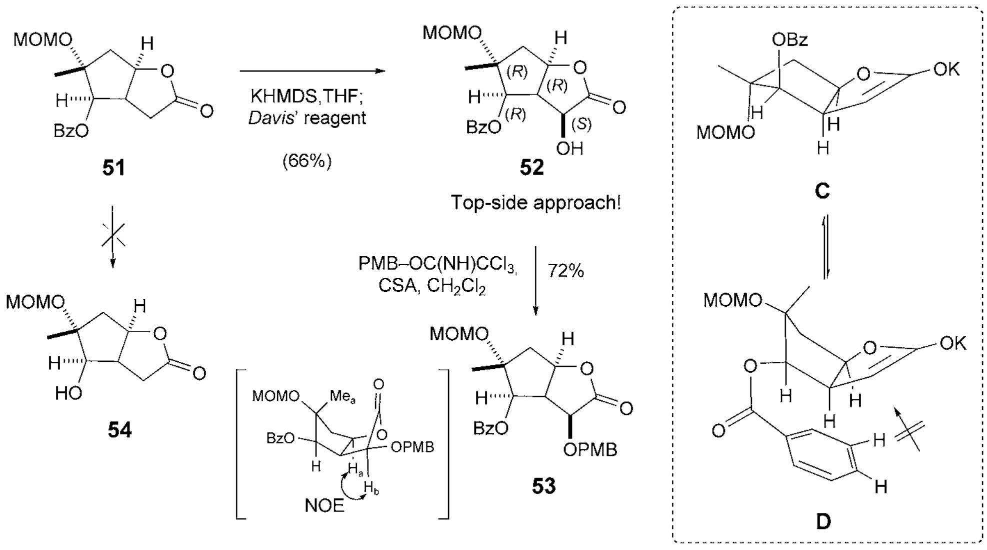
(*Scheme 11*). First, the OH group of **43** was protected as the corresponding methoxymethyl (MOM) ether **49**. The lactone in **49** was opened with pyrrolidine, and the resulting alcohol was protected as benzoyl ester **50**. Removal of the TBS protection group liberated the 5-OH group, which was then used for the formation of the desired lactone **51**.

Scheme 11



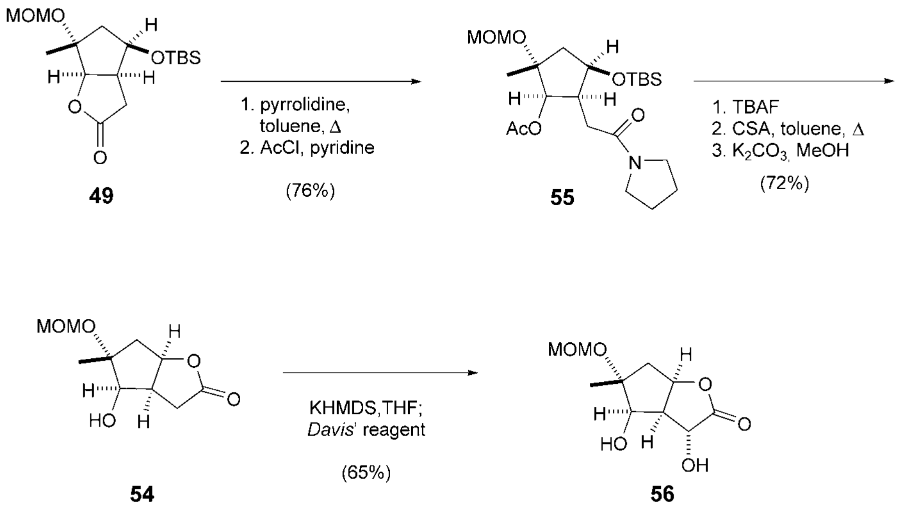
The following step, α-hydroxylation of the lactone moiety of **51**, was investigated next (*Scheme 12*). Once more, we were faced with disappointment, as treatment of **51** with KHMDS, followed by a solution of the *Davis* oxaziridine reagent, afforded alcohol (**52**) with the undesired (*S*)-configuration. The relative configuration of the newly introduced PMB-protected OH group in **53** was confirmed by two-dimensional ^{1}H-NMR NOESY experiments. Among the noted cross-peaks, strong correlations were detected between the H_b-atom, adjacent to the newly introduced PMB-protected OH group, and the ring-fusion H_a-atom. Surprisingly, the *Davis* reagent approached the enolate derived from lactone **51** from the concave β-face of the *cis*-fused system. In an attempt to understand the unexpected stereoselectivity of the hydroxylation, we considered conformers **C** and **D** with molecular models. According to these studies, the attack should have occurred from the convex α-face. The only possibility we could imagine was that **D**, with the benzoyl (Bz) group in pseudo-equatorial position, might be the preferred conformer. Presumably, the Bz group is wrapped around the ring fusion, and lies beneath the enolate, thus blocking the bottom face. Therefore, we sought to attempt the α-hydroxylation on substrate **54** lacking the Bz group. Unfortunately, attempted removal of the Bz group of **51** under basic conditions resulted in complex mixtures, likely due to competing lactone opening. Therefore, an alternative preparation of the desired alcohol **54** was developed, by introducing a 3-(AcO) group (*vide infra*).

Scheme 12. *Stereochemical Course of the* Davis *Hydroxylation of* **51**



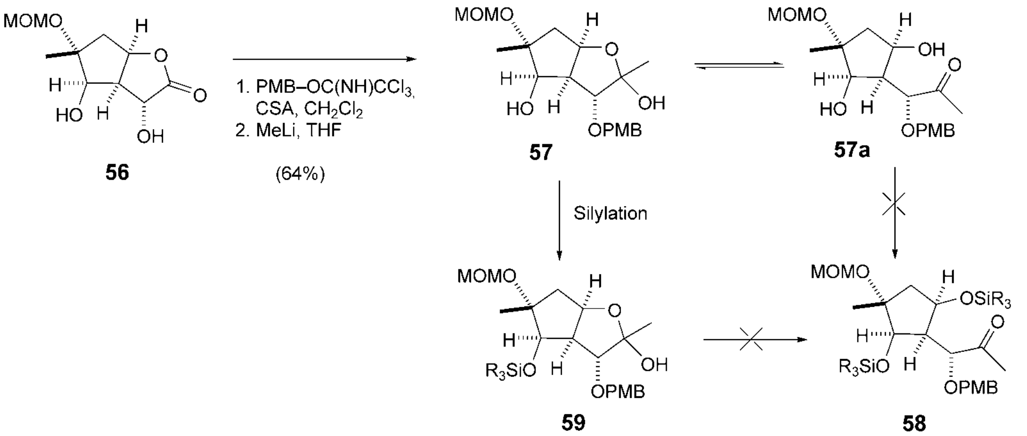
As shown in *Scheme 13*, lactone **49** was treated with pyrrolidine, and the resulting alcohol was acetylated to **55**. The TBS group was removed with Bu_4NF (TBAF), and the lactone was formed. In contrast to the previous Bz protecting group (*vide supra*), the AcO group could be smoothly cleaved to give alcohol **54**. α-Hydroxylation of the latter was then effected by treatment with excess of KHMDS, followed by addition of the *Davis* reagent. In this case, the OH group was successfully introduced from the convex α-face to give alcohol **56** with the desired (R)-configuration.

Scheme 13



With all the stereogenic centers set, the final steps in the synthesis of fragment **A** were investigated. The newly introduced OH group in **56** was protected as the PMB ether (*Scheme 14*). The next step, MeLi addition to the lactone, proceeded smoothly, yielding the hemi-acetal **57** in good yield. We envisaged that **57** would exist in an equilibrium with hydroxy ketone **57a**, and that the latter, under the right conditions, could be trapped as silyl ether **58**. However, in our hands, using a variety of silylating reagents (R_3SiCl, R_3SiTf), we were unable to obtain **58**. The only products were monosilylated compounds of type **59**. Additional attempts to trap the ketone **58**, from these intermediates, also failed.

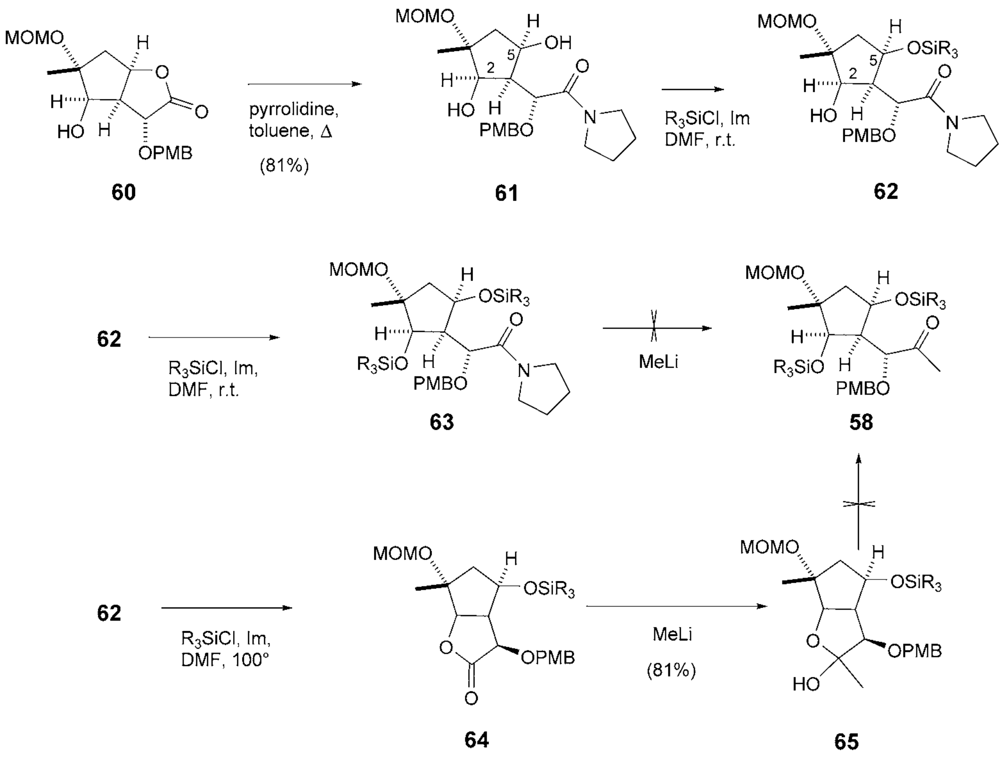
Scheme 14



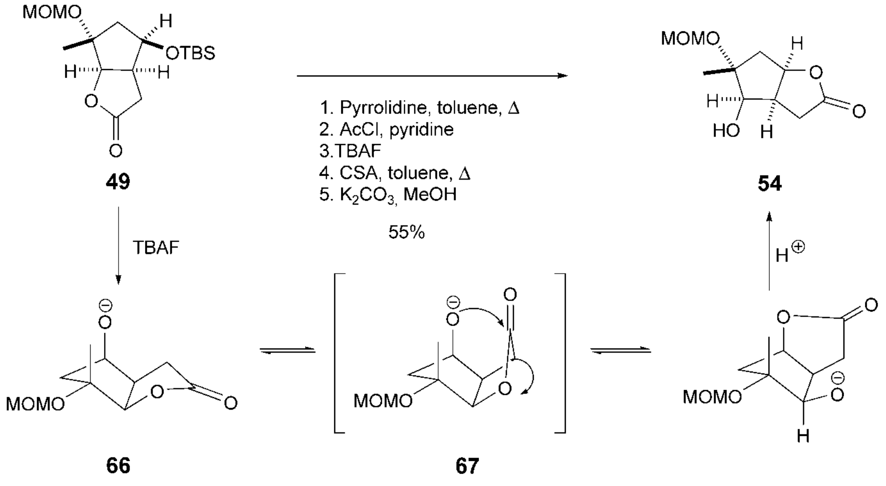
As an alternative to a direct MeLi addition to the lactone derived from **56**, we investigated the possibility of opening this lactone with an amine, and subsequently preparing the desired methyl ketone **58**. Heating **60** with pyrrolidine gave the amide **61**, which was then subjected to various silylating conditions (*Scheme 15*). We were able to introduce larger silyl groups (TBS, TIPS) at the less-hindered 5-position to give **62**, but we were limited to smaller protecting groups such as Me_3Si and Et_3Si (TES) for the more-hindered OH-group at C(2) to give species of type **63**. Attempted protection of the 2-OH group with larger groups under more-forcing conditions simply resulted in lactonization to give **64**. The next step, conversion of the amide to a methyl ketone also proved difficult. Under various conditions, treatment of **63** with MeLi simply resulted in recovered starting material. Since we had samples of **64** on hand, we once again looked for a direct conversion of the lactone unit to the methyl ketone. However, as in the previous examples (*vide supra*), MeLi addition proceeded well to give **65**, but this hemi-acetal could not be trapped as ketone **58**.

Whilst carrying material though the presently favored synthesis-to-date, we were constantly trying to optimize the involved steps. In one particular example, this proved to be quite rewarding (*Scheme 16*). For the requisite transformation of lactone **49** to lactone **54**, a five-step sequence had been developed. However, we were pleased to find that simply treating **49** with TBAF overnight also accomplished the same task in good yield. From a mechanistic point of view, it would seem that the alkoxide generated upon

Scheme 15



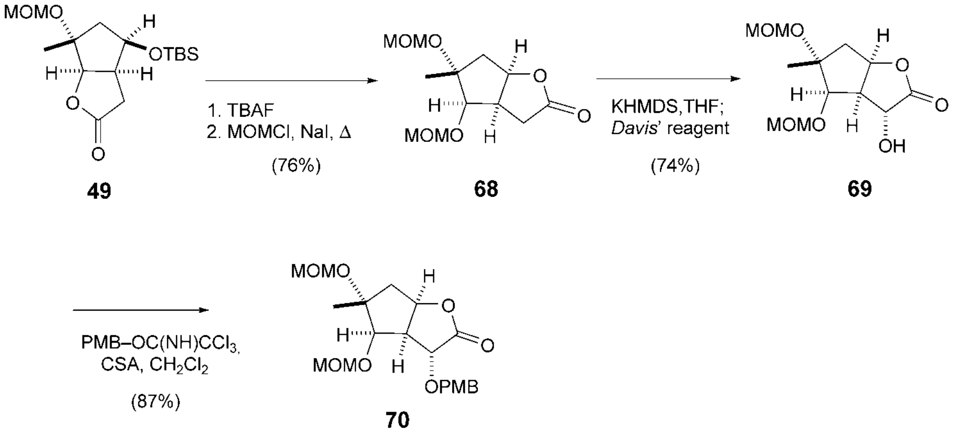
Scheme 16



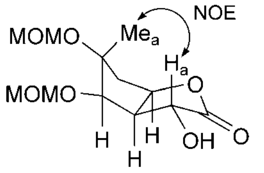
desilylation might exist in two major conformations. On the basis of molecular-model studies, conformer **66** conceivably can undergo an intramolecular lactone-opening to **67**, which reacts to **54**.

In continuing with the scale-up procedure, lactone **49** was converted to lactone **68** *via* the new TBAF procedure (*Scheme 17*). α-Hydroxylation then gave **69**, and subsequent PMB protection afforded **70** in good yield.

Scheme 17



The relative configuration of the newly introduced OH group in **70** was confirmed by ^{1}H-NMR NOESY experiments. Among the observed cross-peaks, strong correlations were noticed between the H_a-atom adjacent to the newly introduced OH group, and the ring Me_a group (*Fig. 2*).

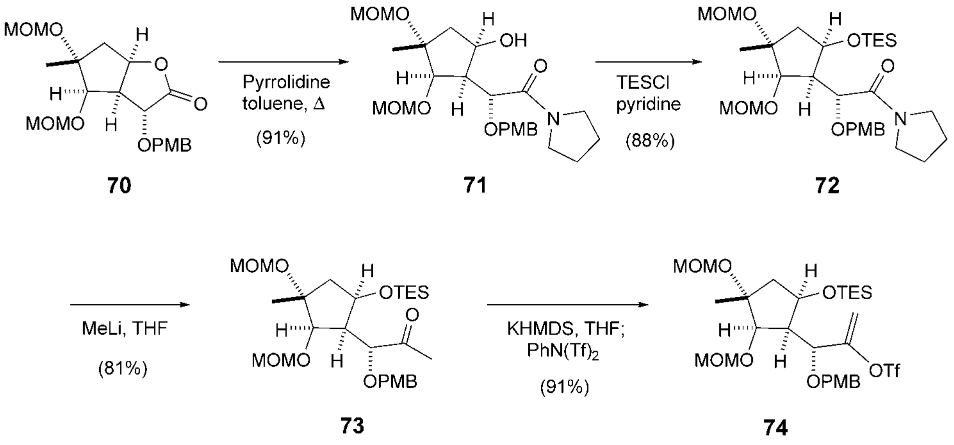


δ(H) 4.59 (*d*, J = 3.3 Hz, H_a)
δ(H) 1.33 (*s*, Me_a)

Fig. 2. *Sole significant NOE effect in compound* **69**

With lactone **70** at hand, we investigated the formation of the requisite methyl ketone (*Scheme 18*). Lactone **70** was opened with pyrrolidine to give **71**, and the resulting alcohol was trapped as TES ether **72**. With a TES ether on one side and a MOM ether on the other, MeLi addition to **72** proceeded smoothly to give methyl ketone **73**. Although more than 2 equiv. of MeLi were required for this reaction to go to completion, no double-addition product was detected. The final step in this sequence, regioselective vinyl triflate formation, was accomplished by first deprotonating the methyl ketone **73** under kinetically controlled conditions, and then treating the resulting enolate with a solution of $PhN(Tf)_2$. The resulting material was fully characterized and shown to be vinyl triflate **74**, the target of the present synthetic study.

Scheme 18



Conclusions. – In summary, we have prepared the highly functionalized building block **74** from the enantiomerically enriched alcohol **44** *via* an eleven-step sequence that involves a highly stereoselective epoxidation and a subsequent intramolecular ring opening reaction. This allowed a quick establishment of the required oxygenation pattern combined with the desired relative configuration at all stereogenic centers. The advanced intermediate **74** trades well for a rational synthetic access to a multitude of jatrophane natural products. The preparation of the coupling partners required for a synthesis of the polyesters pepluanin A (**1**) and euphosalicin (**2**) is currently underway in our laboratories.

Experimental Part

Abbreviations. Ac, acetyl; Bn, benzyl (= phenylmethyl); Bz, benzoyl (= phenylcarbonyl); CSA, chlorosulfonic acid; DIPEA, 'diisopropylethylamine' ($Et(i-Pr)_2N$); DMAP, 4-(dimethylamino)pyridine; DMDO, dimethyldioxirane; DMF, *N*,*N*-dimethylformamide; Im, 1*H*-imidazole; KHMDS, potassium hexamethyldisilazane; MCPBA, 'metachloroperbenzoic acid' (= 3-chlorobenzeneperoxoic acid); MDR, multidrug resistance; MOM, methoxymethyl; MPPA, monoperoxyphthalic acid magnesium salt; Nic, nicotinoyl (= pyridyl-3-carbonyl); PDC, pyridinium dichromate; PG, protecting group; PMB, 'paramethoxybenzyl' (= (4-methoxyphenyl)methyl); TBAF, tetrabutylammonium fluoride (Bu_4NF); TBS, *tert*-butyl(dimethyl)silyl (*t*-$BuMe_2Si$); TES, triethylsilyl (Et_3Si); Tf, trifluoromethylsulfonyl (= CF_3SO_2); THF, tetrahydrofuran; TIPS, triisopropylsilyl (i-Pr_3Si); TMS, trimethylsilyl (Me_3Si).

General. All moisture-sensitive reactions were carried out under Ar atmosphere. Anhydrous (anh.) THF was distilled from Na/benzophenone ketyl. All other solvents were of HPLC grade. Flash chromatography (FC) [18] was performed with *Merck* silica gel (0.04–0.63 mm, 240–400 mesh) under medium pressure. Thin-layer chromatography (TLC) was carried out with *Merck* silica gel *60-F_{254}* plates. Optical rotations were measured on a *Perkin-Elmer P-341* polarimeter. NMR Spectra were recorded on either a *Bruker Avance DPX-250* or *-400* apparatus. Unless otherwise stated, all NMR spectra were recorded in $CDCl_3$ soln. and referenced to the residual $CHCl_3$ signal (δ(H) 7.26, δ(C) 77.0 ppm). Chemical shifts δ are given in ppm, coupling constants *J* are expressed in Hz, and multiplicities are abbreviated as *s*, *singlet*; *d*, *doublet*; *t*, *triplet*; *q*, *quadruplet*; *m*, *multiplet*. Assignments of H-atom resonances were confirmed, when possible, by selective homonuclear decoupling experiments, or by correlated spectroscopy. Electron-impact (EI) mass spectra were measured on a *Micro Mass*

Trio-200 mass spectrometer (*Fisions Instruments*, UK). High-resolution mass spectra (HR-MS) were performed with a *Finnigan MAT-8230* apparatus at a resolution of 10000; in *m*/*z* (rel. %).

*(2*S*)-(Benzyloxy){(1*S*,5*R*)-5-[(4-methoxybenzyl)oxy]-3-methylcyclopent-2-en-1-yl}acetic Acid* (**28**). To a cooled (0°), stirred soln. of **14** (3.0 g, 26.3 mmol) in DMF (60 ml) was portion-wise added NaH (55% suspension in oil; 2.41 g, 55.2 mmol) over 15 min. PMBCl (4.1 g, 26.3 mmol) and Bu_4NI (100 mg, 0.3 mmol) were then added. The resulting dark mixture was allowed to warm to r.t., and stirred for 3 h. The mixture was then added to a 2 : 1 mixture of sat. aq. NH_4Cl soln./Et_2O (300 ml). The resulting layers were separated, and the aq. layer was washed with Et_2O (3 × 100 ml). The volatile components were removed under reduced pressure, and the resulting crude material was dissolved in pyridine (30 ml). 2-(Benzyloxy)acetyl chloride (4.9 g, 26.5 mmol) and DMAP (20 mg, 0.16 mmol) were added, and the resulting mixture was stirred for 18 h. The mixture was diluted with Et_2O (100 ml), and washed with aq. 1N HCl soln. (100 ml), followed by sat. aq. $NaHCO_3$ soln. (2 × 50 ml). The solvents were removed under reduced pressure, and the resulting material was subjected to FC (hexane/AcOEt 5 : 1) to afford the desired 2-(benzyloxy)acetate **20** (7.25 g, 18.9 mmol, 72% yield) as a clear colorless oil. To a cold (– 78°), stirred soln. of **20** (471 mg, 1.23 mmol) and TMSCl (0.67 g, 6.2 mmol) in anh. THF (50 ml) was added a 0.5M soln. of KHMDS in toluene (12.3 ml, 6.2 mmol). The mixture was stirred for 1 h at – 78°, allowed to warm to r.t. over 1 h, and stirred for 2 h at r.t. Then., sat. aq. NH_4Cl soln. (50 ml) was added, and the resulting layers were separated. The aq. layer was extracted with AcOEt (3 × 50 ml), and the combined org. layers were dried ($MgSO_4$). The solvents were removed under reduced pressure, and the resulting material was subjected to FC (hexane/AcOEt/AcOH 60 : 30 : 1) to afford **28** (358 mg, 76%). Clear, colorless oil. ^{1}H-NMR ($CDCl_3$, 400 MHz): 1.75 (*s*, 3 H); 2.35 – 2.55 (*m*, 2 H); 3.28 (br. *s*, 1 H); 3.80 (*s*, 3 H); 4.17 (*d*, *J* = 4.0, 1 H); 4.35 – 4.80 (*m*, 5 H); 5.29 (br. *s*, 1 H); 6.85 (*d*, *J* = 8.7, 2 H); 7.19 (*d*, *J* = 8.7, 2 H); 7.29 – 7.37 (*m*, 5 H); 10.65 (br. s, 1 H). ^{13}C-NMR ($CDCl_3$, 100.6 MHz): 16.1; 42.4; 52.0; 55.3; 71.8; 73.2; 77.9; 79.1; 113.9; 122.1; 127.9; 128.1; 128.4; 129.1; 129.5; 137.5; 140.8; 159.5; 172.7.

*(2*S*)-(Benzyloxy){(1*R*,2*R*,3*R*,5*S*)-3-[(4-methoxybenzyl)oxy]-5-methyl-6-oxabicyclo[3.1.0]hex-2-yl}acetic Acid* (**24**). To a cold (– 15°), stirred soln. of **28** (302 mg, 0.79 mmol) in anh. CH_2Cl_2 (30 ml) was added MCPBA (77%; 177 mg, 0.79 mmol). The mixture was stirred for 30 min at – 15°. Then, sat. aq. $NaHCO_3$ soln. (30 ml) was added, and the resulting layers were separated. The aq. layer was extracted with CH_2Cl_2 (3 × 30 ml), and the combined org. layers were dried ($MgSO_4$). The solvents were removed under reduced pressure, and the resulting material was subjected to FC (hexane/AcOEt/AcOH 50 : 50 : 1) to afford **24** (264 mg, 84%). Colorless solid. ^{1}H-NMR ($CDCl_3$, 400 MHz): 1.43 (*s*, 3 H); 1.83 (*dd*, *J* = 15.1, 6.5, 1 H); 2.14 (*d*, *J* = 15.1, 1 H); 2.66 (br. *t*, *J* = 8.3, 1 H); 3.31 (br. *s*, 1 H); 3.77 (*s*, 3 H); 4.03 (*dd*, *J* = 6.7, 6.5, 1 H); 4.33 (*d*, *J* = 11.7, 1 H); 4.42 – 4.48 (*m*, 3 H); 4.66 (*d*, *J* = 10.9, 1 H); 6.80 (*d*, *J* = 8.7, 2 H); 7.18 (*d*, *J* = 8.7, 2 H); 7.27 – 7.35 (*m*, 5 H); 8.96 (br. *s*, 1 H). ^{13}C-NMR ($CDCl_3$, 100.6 MHz): 17.5; 38.0; 49.6; 55.2; 62.7; 63.6; 71.9; 72.8; 75.7; 76.7; 113.7; 127.8; 128.0; 128.3; 129.4; 129.9; 137.4; 159.1; 175.9. X-Ray crystal structure: see *Fig. 1* and crystallographic section below.

*2-[(1*S*,5*R*)-5-{[*tert*-Butyl(dimethyl)silyl]oxy}-3-methylcyclopent-2-en-1-yl]-*N*,*N*-dimethylacetamide* (**34**). To a stirred soln. of alcohol **44** (13.9 g, 61.0 mmol) in toluene (30 ml), *N*,*N*-dimethylacetamide dimethoxy acetal (24.6 g, 183 mmol) was added dropwise. The mixture was heated to reflux for 48 h, during which time the generated MeOH was allowed to distill out. The volatiles were removed under reduced pressure, and the resulting crude material was purified by FC (hexane/AcOEt 5 : 1) to afford **34** (15.5 g, 85%). Clear, yellow oil. R_f 0.31 (hexane/AcOEt 2 : 1). $[\alpha]_D^{20} = +24.4$ (c = 1.1, acetone). IR (film): 3035, 2929, 2856, 1652, 1471, 1397. ^{1}H-NMR ($CDCl_3$, 400 MHz): 0.01 (*s*, 3 H); 0.03 (*s*, 3 H); 0.86 (*s*, 9 H); 1.68 (*s*, 3 H); 2.10 – 2.25 (*m*, 2 H); 2.43 (*dd*, *J* = 16.0, 6.7, 1 H); 2.62 (*dd*, *J* = 16.0, 6.8, 1 H); 2.92 (*s*, 3 H); 2.97 (*s*, 3 H); 3.09 – 3.17 (*m*, 1 H); 4.48 – 4.54 (*m*, 1 H); 5.25 – 5.30 (*m*, 1 H). ^{13}C-NMR ($CDCl_3$, 100.6 MHz): – 5.1; – 4.7; 17.0; 18.1; 25.8; 32.3; 35.3; 37.1; 45.6; 46.1; 73.6; 127.0; 137.7; 172.8. EI-MS (70 eV): 297 (1, M^+), 240 (42), 72 (100). HR-EI-MS (70 eV): 297.2127 (M^+, $C_{16}H_{31}NO_2Si^+$; calc. 297.2124).

*(3a*S*,4*R*,6*R*,6a*R*)-4-{[*tert*-Butyl(dimethyl)silyl]oxy}-3,3a,4,5,6,6a-hexahydro-6-hydroxy-6-methyl-2*H*-cyclopenta[*b*]furan-2-one* (**43**). To a cooled (0°), stirred soln. of **34** (15.0 g, 50.3 mmol) and 18-crown-6 (1.0 g, 3.8 mmol) in a 1 : 1 : 1 mixture of CH_2Cl_2/acetone/H_2O (450 ml) was added $NaHCO_3$ (32.0 g, 381 mmol) portionwise over 20 min. A soln. of *Oxone* (= potassium peroxymonosulfate; 60.0 g, 100 mmol) in H_2O (300 ml) was added dropwise over 1 h. The resulting mixture was stirred for another 2 h at 0°. Then, AcOEt (200 ml) was added, and the layers were separated. The aq. layer was extracted with AcOEt (2 × 200 ml), and the combined org. layers were dried ($MgSO_4$). The solvents were removed under reduced pressure, and the resulting material was subjected to FC (hexane/AcOEt 2 : 1) to afford **43** (11.5 g, 80%). Clear, colorless oil. R_f 0.17 (hexane/AcOEt 2 : 1). $[\alpha]_D^{20} = -26.6$ (c = 0.95, acetone). IR (film): 3440, 2957, 2931, 1778, 1472. ^{1}H-NMR ($CDCl_3$, 400 MHz): 0.04 (*s*, 6 H); 0.88 (*s*, 9 H); 1.40 (*s*, 3 H); 1.53 – 1.65 (*m*, 2 H); 1.97 (*dd*, *J* = 13.6, 6.3, 1 H); 2.44 (*dd*, *J* = 18.8, 10.9, 1 H); 2.98 (*dd*, *J* = 18.8, 2.9, 1 H); 3.09 – 3.18 (*m*, 1 H); 4.41 (*dd*, *J* = 6.6, 1.5, 1 H);

4.52–4.59 (*m*, 1 H). ^{13}C-NMR ($CDCl_3$, 100.6 MHz): -5.0; -4.8; 18.0; 23.6; 25.7; 28.0; 41.4; 45.3; 71.1; 78.4; 89.9; 177.6. EI-MS (70 eV): 229 (41), [$M-{}^tBu$]$^+$), 137 (42), 75 (100). HR-EI-MS (70 eV): 229.0901 ([$M-{}^tBu$]$^+$), $C_{10}H_{17}O_4Si^+$; calc. 229.0896).

*(3a*S*,4*R*,6*R*,6a*R*)-4-{[*tert*-Butyl(dimethyl)silyl]oxy}-3,3a,4,5,6,6a-hexahydro-6-(methoxymethoxy)-6-methyl-2*H*-cyclopenta[*b*]furan-2-one* (**49**). To a cooled (0°), stirred soln. of **43** (11.2 g, 39.3 mmol) and DIPEA (25.2 g, 194 mmol) in anh. CH_2Cl_2 (100 ml) was dropwise added MOMCl (9.50 g, 118 mmol) over 15 min. The resulting mixture was allowed to warm to r.t. and stirred for 48 h. Then, sat. aq. $NaHCO_3$ soln. (25 ml) was added, and the layers were separated. The aq. layer was extracted with CH_2Cl_2 (3 × 50 ml), and the combined org. layers were dried ($MgSO_4$). The solvents were removed under reduced pressure, and the resulting material was subjected to FC (hexane/AcOEt 3:1) to afford **49** (10.5 g, 81%). Clear, colorless oil. R_f 0.39 (hexane/AcOEt 2:1). $[\alpha]^{20}_D = -21.3$ ($c = 1.2$, acetone). IR (film): 2957, 2823, 1789, 1471. ^{1}H-NMR ($CDCl_3$, 400 MHz): 0.05 (*s*, 6 H); 0.88 (*s*, 9 H); 1.37 (*s*, 3 H); 1.50 (*dd*, $J = 13.9$, 9.3, 1 H); 2.18 (*dd*, $J = 13.9$, 6.4, 1 H); 2.45 (*dd*, $J = 18.7$, 10.9, 1 H); 2.98 (*dd*, $J = 18.7$, 2.9, 1 H); 3.05–3.08 (*m*, 1 H); 3.37 (*s*, 3 H); 4.50 (*ddd*, $J = 9.3$, 8.3, 6.4, 1 H); 4.58 (*dd*, $J = 6.6$, 1.5, 1 H); 4.65–4.70 (*m*, 2 H). ^{13}C-NMR ($CDCl_3$, 100.6 MHz): -5.1; -4.7; 18.0; 18.9; 25.7; 28.0; 41.4; 43.7; 55.7; 71.0; 83.8; 88.5; 91.3; 177.4. EI-MS (70 eV): 273 (21, [$M-{}^tBu$]$^+$), 243 (100). HR-EI-MS (70 eV): 273.1161 ([$M-{}^tBu$]$^+$, $C_{12}H_{21}O_5Si^+$; calc. 273.1158).

*(3*S*,4*R*,5*R*,6a*R*)-3,3a,4,5,6,6a-Hexahydro-3-[(4-methoxybenzyl)oxy]-5-(methoxymethoxy)-5-methyl-2-oxo-2*H*-cyclopenta[*b*]furan-4-yl Benzoate* (**53**). To a stirred soln. of **52** (618 mg, 1.83 mmol) in anh. CH_2Cl_2 (25 ml) was added PMB–OC(=NH)CCl_3 (780 mg, 2.74 mmol) and CSA (42 mg, 0.18 mmol). The resulting mixture was stirred for 18 h at r.t. Then, sat. aq. $NaHCO_3$ soln. (10 ml) was added, and the resulting layers were separated. The aq. layer was extracted with CH_2Cl_2 (3 × 20 ml), and the combined org. layers were dried ($MgSO_4$). The solvents were removed under reduced pressure, and the resulting material was subjected to FC (hexane/AcOEt 2:1) to afford **53** (698 mg, 72%). Clear, colorless oil. ^{1}H-NMR ($CDCl_3$, 400 MHz): 1.30 (*s*, 3 H); 2.13 (*dd*, $J = 3.2$, 15.5, 1 H); 2.67 (*ddd*, $J = 1.3$, 7.3, 15.4, 1 H); 3.36 (*s*, 3 H); 3.37–3.42 (*m*, 1 H); 3.78 (*s*, 3 H); 4.34 (*d*, $J = 8.9$, 1 H); 4.57–4.75 (*m*, 4 H); 4.93 (*ddd*, $J = 3.2$, 6.8, 6.9, 1 H); 5.69 (*d*, $J = 4.6$, 1 H); 6.80 (*d*, $J = 8.7$, 2 H); 7.18 (*d*, $J = 8.6$, 2 H); 7.45 (br. *t*, $J = 7.6$, 2 H); 7.56 (br. *t*, $J = 7.4$, 2 H); 7.93–7.97 (*m*, 1 H). ^{13}C-NMR ($CDCl_3$, 100.6 MHz): 17.9; 44.9; 46.1; 55.2; 55.8; 72.4; 72.5; 77.4; 80.3; 87.7; 91.6; 113.8; 128.4; 128.7; 128.8; 129.4; 129.8; 129.9; 133.2; 159.5; 165.1; 174.6.

*(3a*S*,4*R*,5*R*,6a*R*)-3,3a,4,5,6,6a-Hexahydro-4-hydroxy-5-(methoxymethoxy)-5-methyl-2*H*-cyclopenta[*b*]furan-2-one* (**54**). To a stirred soln. of **49** (9.50 g, 28.8 mmol) in anh. THF (40 ml) was added TBAF (1M soln. in THF; 43.2 ml, 43.2 mmol). The mixture was stirred at r.t. for 18 h. The solvent was removed under reduced pressure, and the resulting crude was subjected to FC (hexane/AcOEt 1:1) to afford **54** (5.47 g, 88%). Clear, colorless oil. R_f 0.3 (AcOEt). $[\alpha]^{20}_D = -15.1$ ($c = 1.2$, $CDCl_3$). IR (film): 3443, 2940, 2825, 1769, 1644, 1454. ^{1}H-NMR ($CDCl_3$, 400 MHz): 1.35 (*s*, 3 H); 2.03 (*dd*, $J = 14.8$, 3.5, 1 H); 2.39 (*dd*, $J = 14.8$, 6.8, 1 H); 2.56 (*dd*, $J = 18.4$, 11.1, 1 H); 2.60 (br. *s*, 1 H); 2.81 (*dd*, $J = 18.4$, 2.8, 1 H); 3.18–3.26 (*m*, 1 H); 3.38 (*s*, 3 H); 3.97 (*dd*, $J = 6.5$, 2.6, 1 H); 4.63 (*d*, $J = 7.6$, 1 H); 4.75 (*d*, $J = 7.6$, 1 H); 4.99 (*ddd*, $J = 7.5$, 6.8, 3.5, 1 H). ^{13}C-NMR ($CDCl_3$, 100.6 MHz): 17.8; 28.7; 41.3; 42.4; 55.8; 77.9; 83.2; 86.7; 91.3; 177.9. EI-MS (70 eV): 216 (1, M^+), 171 (46), 153 (65), 57 (100). HR-EI-MS (70 eV): 216.0993 (M^+, $C_{10}H_{16}O_5^+$; calc. 216.0998).

*(3a*S*,4*R*,5*R*,6a*R*)-3,3a,4,5,6,6a-Hexahydro-4,5-bis(methoxymethoxy)-5-methyl-2*H*-cyclopenta[*b*]furan-2-one* (**68**). To a cooled (0°), stirred soln. of **54** (950 mg, 4.40 mmol) and DIPEA (2.84 g, 22.0 mmol) in anh. CH_2Cl_2 (20 ml) was dropwise added MOMCl (1.06 g, 13.2 mmol) over 15 min. Then, NaI (20 mg, 0.13 mmol) was added, and the resulting mixture was heated at reflux for 18 h. The mixture was allowed to cool to r.t., sat. aq. $NaHCO_3$ soln. (10 ml) was added, and the layers were separated. The aq. layer was extracted with CH_2Cl_2 (3 × 20 ml), and the combined org. layers were dried ($MgSO_4$). The solvents were removed under reduced pressure, and the resulting material was subjected to FC (hexane/AcOEt 1:1) to afford **68** (984 mg, 86%). Clear, colorless oil. R_f 0.38 (AcOEt). $[\alpha]^{20}_D = +28.5$ ($c = 1.1$, $CDCl_3$). IR (film): 2947, 2896, 1772, 1451. ^{1}H-NMR ($CDCl_3$, 400 MHz): 1.36 (*s*, 3 H); 1.93 (*dd*, $J = 14.8$, 4.2, 1 H); 2.44 (*ddd*, $J = 14.8$, 7.2, 1.3, 1 H); 2.58 (*dd*, $J = 18.0$, 10.1, 1 H); 2.68 (*dd*, $J = 18.0$, 2.8, 1 H); 3.10–3.25 (*m*, 1 H); 3.33 (*s*, 3 H); 3.41 (*s*, 3 H); 3.86 (*d*, $J = 5.8$, 1 H); 4.55–4.70 (*m*, 4 H); 4.97 (*dd*, $J = 7.5$, 7.5, 4.3 1 H). ^{13}C-NMR ($CDCl_3$, 100.6 MHz): 18.4; 29.5; 41.6; 42.7; 55.7; 56.6; 83.7; 85.3; 87.3; 91.4; 98.2; 177.5. EI-MS (70 eV): 260 (2, M^+), 240 (25), 215 (74), 198 (100). HR-EI-MS (70 eV): 260.1264 (M^+, $C_{12}H_{20}O_6^+$; calc. 260.1260).

*(3*R*,3a*S*,4*R*,5*R*,6a*R*)-3,3a,4,5,6,6a-Hexahydro-3-hydroxy-4,5-bis(methoxymethoxy)-5-methyl-2*H*-cyclopenta[*b*]furan-2-one* (**69**). To a cooled (−78°), stirred soln. of lactone **68** (850 mg, 3.27 mmol) in anh. THF (40 ml) was added a 0.5M soln. of KHMDS in toluene (9.80 ml, 4.90 mmol). The mixture was stirred for 1 h at −78°. Then. a cold (−78°) soln. of *Davis* reagent (=3-(3-nitrophenyl)-2-(phenylsulfonyl)-1,2-oxaziridine; 1.28 g, 4.90 mmol) in anh. THF (5 ml) was added *via* a cannula. The mixture was stirred for an additional 30 min

at $-78°$. Then, a soln. of CSA (1.14 g, 4.90 mmol) in anh. THF (5 ml) was added *via* a cannula, and the resulting mixture was allowed to warm to r.t. over 1 h. Then, sat. aq. NH_4Cl soln. (15 ml) was added, the layers were separated, and the aq. layer was extracted with AcOEt (3 × 20 ml). The combined org. layers were dried ($MgSO_4$) and evaporated under reduced pressure. The resulting material was subjected to FC (hexane/AcOEt 1:1) to afford **69** (665 mg, 74%). Clear, colorless oil. R_f 0.36 (AcOEt). $[\alpha]_D^{20} = +21.6$ ($c = 1.1$, $CDCl_3$). IR (film): 3385, 2948, 1770, 1640, 1567, 1447. ^{1}H-NMR ($CDCl_3$, 400 MHz): 1.33 (*s*, 3 H); 1.86 (*dd*, $J = 14.5, 5.2$, 1 H); 2.42 (*dd*, $J = 14.5, 7.2, 1.3$, 1 H); 2.88 (br. *s*, 1 H); 3.16 (*ddd*, $J = 7.9, 6.6, 3.3$, 1 H); 3.35 (*s*, 3 H); 3.42 (*s*, 3 H); 4.08 (*dd*, $J = 6.6, 1.1$, 1 H); 4.59 (*d*, $J = 3.3$, 1 H); 4.65–4.72 (*m*, 4 H); 5.10 (*ddd*, $J = 7.9, 7.2, 5.2$, 1 H). ^{13}C-NMR ($CDCl_3$, 100.6 MHz): 18.4; 42.2; 49.7; 55.8; 56.5; 68.9; 82.1; 83.4; 87.0; 91.4; 97.9; 177.6. EI-MS (70 eV): 276 (2, M^+), 231 (25), 214 (51), 77 (100). HR-EI-MS (70 eV): 276.1217 (M^+, $C_{12}H_{20}O_7^+$; calc. 276.1209).

*(3*R*,3a*R*,4*R*,5*R*,6a*R*)-3,3a,4,5,6,6a-Hexahydro-3-[(4-methoxybenzyl)oxy]-4,5-bis(methoxymethoxy)-5-methyl-2*H*-cyclopenta[*b*]furan-2-one* (**70**). To a stirred soln. of **69** (505 mg, 1.83 mmol) in anh. CH_2Cl_2 (25 ml) was added PMB–OC(=NH)CCl_3 (780 mg, 2.74 mmol) and CSA (42 mg, 0.18 mmol). The resulting mixture was stirred for 18 h at r.t. Then, sat. aq. $NaHCO_3$ soln. (10 ml) was added, and the resulting layers were separated. The aq. layer was extracted with CH_2Cl_2 (3 × 20 ml), and the combined org. layers were dried ($MgSO_4$) and evaporated under reduced pressure. The resulting material was subjected to FC (hexane/AcOEt 2:1) to afford **70** (630 mg, 87%). Clear, colorless oil. R_f 0.16 (hexane/AcOEt 2:1). $[\alpha]_D^{20} = +48.6$ ($c = 1.1$, $CDCl_3$). IR (film): 3277, 2948, 1769, 1731, 1613, 1586, 1447. ^{1}H-NMR ($CDCl_3$, 400 MHz): 1.32 (*s*, 3 H); 1.90 (*dd*, $J = 14.9, 4.3$, 1 H); 2.44 (*ddd*, $J = 14.9, 7.3, 1.2$, 1 H); 3.12 (*ddd*, $J = 7.4, 5.9, 1.5$, 1 H); 3.30 (*s*, 3 H); 3.32 (*s*, 3 H); 3.80 (*s*, 3 H); 3.97 (*d*, $J = 6.3$, 1 H); 4.20 (*d*, $J = 1.5$, 1 H); 4.4–4.8 (*m*, 6 H); 5.10 (*ddd*, $J = 7.4, 7.4, 4.2$, 1 H); 6.9 (*d*, $J = 8.6$, 2 H); 7.3 (*d*, $J = 8.6$, 2 H). ^{13}C-NMR ($CDCl_3$, 100.6 MHz): 18.2; 42.4; 49.5; 55.3; 55.8; 56.6; 71.7; 74.4; 82.9; 84.3; 87.4; 91.4; 98.0; 113.9; 129.2; 130.1; 159.5; 175.0. EI-MS (70 eV): 396 (1, M^+), 275 (3), 137 (24), 121 (100). HR-EI-MS (70 eV): 396.1775 (M^+, $C_{20}H_{28}O_8^+$; calc. 396.1786).

*(1*R*,2*R*,3*R*,4*R*)-2-{(1*R*)-1-[(4-Methoxybenzyl)oxy]-2-oxo-2-pyrrolidin-1-ylethyl}-3,4-bis(methoxymethoxy)-4-methylcyclopentanol* (**71**). To a stirred soln. of **70** (504 mg, 1.27 mmol) in anh. toluene (5 ml) was added pyrrolidine (524 µl, 6.40 mmol). The resulting mixture was heated to reflux for 18 h. The mixture was allowed to cool to r.t., and the volatiles were removed under reduced pressure. The resulting crude material was subjected to FC (AcOEt) to afford **71** (541 mg, 91%), with trace-amounts of pyrrolidine. Clear, orange oil. R_f 0.1 (AcOEt). $[\alpha]_D^{20} = -13.3$ ($c = 1.0$, $CDCl_3$). IR (film): 3450, 2957, 2882, 1774, 1631, 1514, 1449. ^{1}H-NMR ($CDCl_3$, 400 MHz): 1.44 (*s*, 3 H); 1.72–1.95 (*m*, 5 H); 2.44 (*dd*, $J = 14.6, 7.1$, 1 H); 2.77 (*m*, 1 H); 3.31 (*s*, 3 H); 3.32–3.38 (*m*, 1 H); 3.40 (*s*, 3 H); 3.45–3.60 (*m*, 4 H); 3.79 (*s*, 3 H); 4.03 (*d*, $J = 3.8$, 1 H); 4.12–4.20 (*m*, 1 H); 4.40 (*d*, $J = 10.9$, 1 H); 4.48 (*d*, $J = 10.9$, 1 H); 4.53 (*d*, $J = 11.1$, 1 H); 4.62–4.69 (*m*, 3 H); 4.76 (*d*, $J = 6.6$, 1 H); 6.86 (br. *d*, $J = 8.8$, 2 H); 7.24 (br. *d*, $J = 8.8$, 2 H). ^{13}C-NMR ($CDCl_3$, 100.6 MHz): 21.0; 23.9; 26.8; 46.7; 46.9; 48.2; 50.0; 55.7; 55.9; 57.0; 71.2; 72.9; 76.9; 86.8; 86.9; 91.9; 99.0; 114.2; 129.7; 130.0; 159.7; 171.2. EI-MS (70 eV): 422 (1, $[M - \mathrm{MOM}]^+$), 210 (13), 137 (27), 121 (100). HR-EI-MS (70 eV): 422.2191 ($[M - \mathrm{MOM}]^+$, $C_{22}H_{32}NO_7^+$; calc. 422.2179).

*1-{(2*R*)-2-{(1*R*,2*R*,3*R*,5*R*)-2,3-Bis(methoxymethoxy)-3-methyl-5-[(triethylsilyl)oxy]cyclopentyl}-2-[(4-methoxybenzyl)oxy]acetyl}pyrrolidine* (**72**). To a stirred soln. of **71** (392 mg, 0.840 mmol) in anh. CH_2Cl_2 (10 ml) was first added pyridine (200 µl, 2.5 mmol), then TESCl (212 µl, 1.26 mmol), and the resulting mixture was stirred at r.t. for 1 h. Then, sat. aq. NH_4Cl soln. (5 ml) was added, and the layers were separated. The aq. layer was extracted with CH_2Cl_2 (3 × 10 ml), and the combined org. layers were dried ($MgSO_4$) and evaporated under reduced pressure. The resulting material was subjected to FC (hexane/AcOEt 2:1) to afford **72** (430 mg, 88%). Clear, colorless oil. R_f 0.21 (hexane/AcOEt 2:1). $[\alpha]_D^{20} = -34.0$ ($c = 0.6$, $CDCl_3$). IR (film): 3854, 3822, 1646, 1613, 1586, 1441. ^{1}H-NMR ($CDCl_3$, 400 MHz): 0.51 (*q*, $J = 7.9$, 6 H); 0.91 (*t*, $J = 7.9$, 9 H); 1.40 (*s*, 3 H); 1.73 (*dd*, $J = 13.8, 5.4$, 1 H); 1.75–1.95 (*m*, 4 H); 2.38 (*dd*, $J = 13.8, 6.8$, 1 H); 3.28–3.35 (*m*, 1 H); 3.38 (*s*, 3 H); 3.39 (*s*, 3 H); 3.40–3.55 (*m*, 3 H); 3.58–3.68 (*m*, 1 H); 3.78 (*s*, 3 H); 3.85 (*d*, $J = 4.3$, 1 H); 4.29 (*d*, $J = 10.8$, 1 H); 4.49 (*d*, $J = 10.8$, 1 H); 4.51–4.58 (*m*, 1 H); 4.61–4.72 (*m*, 4 H); 4.83 (*d*, $J = 6.3$, 1 H); 6.84 (*d*, $J = 8.7$, 2 H); 7.20 (*d*, $J = 8.7$, 2 H). ^{13}C-NMR ($CDCl_3$, 100.6 MHz): 4.8; 6.8; 19.7; 24.2; 26.1; 45.3; 45.5; 45.8; 47.6; 55.2; 55.7; 56.4; 66.6; 72.6; 73.7; 85.2; 86.3; 91.4; 98.44; 113.6; 129.3; 130.9; 158.9; 168.3. EI-MS (70 eV): 582 (2, M^+), 552 (9, $[M - \mathrm{Et}]^+$), 324 (34), 121 (100). HR-EI-MS (70 eV): 552. 2881 ($[M - \mathrm{Et}]^+$, $C_{28}H_{46}NO_8Si^+$, calc. 552.2883).

*(1*R*)-1-[(1*R*,2*R*,3*R*,5*R*)-2,3-Bis(methoxymethoxy)-3-methyl-5-[(triethylsilyl)oxy]cyclopentyl]-1-[(4-methoxyphenyl)methoxy]propan-2-one* (**73**). To a cooled (0°), stirred soln. of **72** (362 mg, 0.623 mmol) in anh. THF (10 ml) was dropwise added a 1.6M soln. of MeLi in Et_2O (0.780 ml, 1.24 mmol) over 30 min. The mixture was stirred for an additional 15 min at 0°. Then, sat. aq. NH_4Cl soln. (5 ml) was added, the aq. layer was extracted with AcOEt (3 × 10 ml), and the combined org. layers were dried ($MgSO_4$) and evaporated under reduced pressure. The resulting material was subjected to FC (hexane/AcOEt 5:1) to afford **73** (265 mg, 81%). Colorless

oil. R_f 0.42 (hexane/AcOEt 2 :1). $[\alpha]_D^{20} = -5.5$ (c = 1.7, $CDCl_3$). IR (film): 2955, 2878, 1715, 1613, 1586, 1515, 1458. ^{1}H-NMR ($CDCl_3$, 400 MHz): 0.58 (q, J = 8.0, 6 H); 0.95 (t, J = 8.0, 9 H); 1.34 (s, 3 H); 1.82 (dd, J = 13.6, 7.6, 1 H); 2.20 – 2.29 (m, 4 H); 3.00 (m, 1 H); 3.33 (s, 3 H); 3.35 (s, 3 H); 3.80 (s, 3 H); 3.98 (d, J = 5.8, 1 H); 4.18 (d, J = 7.8, 1 H); 4.38 (ddd, J = 7.6, 7.5, 7.3, 1 H); 4.42 (s, 2 H); 4.52 – 4.72 (m, 4 H); 6.87 (d, J = 8.6, 2 H); 7.25 (d, J = 8.6, 2 H). ^{13}C-NMR ($CDCl_3$, 100.6 MHz): 4.8; 6.7; 20.0; 26.9; 47.0; 49.0; 55.2; 55.4; 56.3; 70.8; 71.1; 81.4; 85.1; 86.0; 91.5; 97.8; 113.8; 129.5; 130.1; 159.2; 210.0. EI-MS (70 eV): 497 (0.5, $[M - MeO]^+$), 465 (1), 390 (3), 121 (100). HR-EI-MS (70 eV): 497.2559 ($[M - MeO]^+$, $C_{25}H_{41}O_8Si^+$; calc. 497.2571).

*1-{(*R*)-{(1*S*,2*R*,3*R*,5*R*)-2,3-Bis(methoxymethoxy)-3-methyl-5-[(triethylsilyl)oxy]cyclopentyl}[(4-methoxybenzyl)oxy]methyl}ethenyl Trifluoromethanesulfonate* (**74**). To a cooled (– 78°), stirred soln. of **73** (201 mg, 0.381 mmol) in anh. THF (10 ml) was added a 0.5M soln. of KHMDS in toluene (0.84 ml, 0.42 mmol), and the mixture was stirred for 1 h at – 78°. Then, a cold (– 78°) soln. of $PhN(Tf)_2$ (204 mg, 0.57 mmol) in anh. THF (1 ml) was added *via* a cannula. The mixture was stirred for an additional 10 min at – 78°, and then allowed to warm to r.t. over 1 h. Then, sat. aq. NH_4Cl soln. (5 ml) was added, and the resulting layers were separated. The aq. layer was extracted with AcOEt (3 × 10 ml), and the combined org. layers were dried ($MgSO_4$). The solvents were removed under reduced pressure, and the resulting material was subjected to FC (hexane/AcOEt/Et_3N 50 :10 :1) to afford **74** (229 mg, 91%). Clear, colorless oil. R_f 0.55 (hexane/AcOEt 2 :1). $[\alpha]_D^{20} = -3.3$ (c = 0.9, $CDCl_3$). IR (film): 2956, 1664, 1613, 1515, 1443, 1417. ^{1}H-NMR ($CDCl_3$, 400 MHz): 0.56 (q, J = 7.9, 6 H); 0.96 (t, J = 7.9, 9 H); 1.39 (s, 3 H); 1.77 (dd, J = 14.2, 4.2, 1 H); 2.39 (dd, J = 14.2, 6.4, 1 H); 2.71 – 2.78 (m, 1 H); 3.31 (s, 3 H); 3.38 (s, 3 H); 3.79 (s, 3 H); 3.89 (d, J = 4.5, 1 H); 4.18 (d, J = 10.1, 1 H); 4.32 (d, J = 10.4, 1 H); 4.37 (ddd, J = 6.9, 6.4, 4.2, 1 H); 4.59 – 4.71 (m, 5 H); 5.24 (d, J = 3.4, 1 H); 5.39 (d, J = 3.4, 1 H); 6.86 (br. d, J = 8.6, 2 H); 7.28 (br. d, J = 8.6, 2 H). ^{13}C-NMR ($CDCl_3$, 100.6 MHz): 4.9; 6.8; 20.0; 48.3; 48.5; 55.2; 55.5; 56.3; 69.9; 71.6; 76.6; 85.9; 86.7; 91.4; 98.9; 108.5; 113.7; 118.4 (q, F_3C); 129.5; 129.9; 152.7; 159.1. EI-MS (70 eV): 613 (1, $M - MOM]^+$), 283 (3), 181 (5), 135 (8), 121 (100). HR-EI-MS (70 eV): 613.2097 ($[M - MOM]^+$, $C_{26}H_{40}F_3O_9SSi^+$; calc. 613.2114).

X-Ray Crystal-Structure Analysis of **24**^{3}). Formula, $C_{23}H_{26}O_6$; M_r 398.461; crystal system, monoclinic; cell constants: $a = 17.858(4)$, $b = 5.2318(10)$, $c = 22.836(5)$ Å, $\beta = 107.91(3)°$, $V = 2030.2(7)$ Å^3; space group, $P2_1/c$; $Z = 4$; $F(000) = 848$, $\rho_{calc.} = 1.304$ g/cm^3; crystal size 0.03 × 0.11 × 0.56 mm; MoK_α radiation ($\lambda = 07107$ Å); exper. absorption coefficient, 0.09 mm^{-1}; temperature, 120 K; data collection, *Nonius Kappa CCD* instrument; $dx = 35$ mm, ω scans with 450 frames, scan width of 1.5°; data-collection range, $2\theta = 7.0$ to 50.0° (h – 20, 20; k – 5, 6; l – 27, 26); number of reflections collected, 7004; unique reflections, 3587; unique reflections with $F_o > 2\sigma(F_o)$, 2783; no absorption corrections; least-squares refinement; number of parameters refined, 367; largest δ/σ, final cycle < 0.001; extinction correction, largest residual peaks (e/A^3) – 0.16/0.19; final R value, 0.0327; $R_w = 0.0869$, $S = 1.03$.

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^{3}) The crystallographic data of **24** were deposited with the *Cambridge Crystallographic Data Centre* as CCDC-262614. The data can be obtained, free of charge, *via* the internet at http://www.ccdc.cam.ac.uk/data_request/cif.

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Received February 27, 2005