29. Total Synthesis of Crenulatan Diterpenes: Strategy and Stereocontrolled Construction of a Bicyclic Keto-Lactone Building Block

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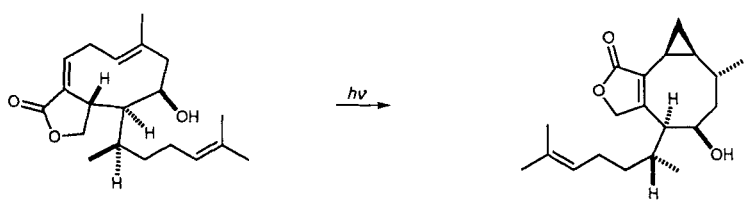
The bicyclic keto lactone **26** was synthesized for the purpose of developing a viable route to marine diterpenes of the crenulatan type. Following the efficient conversion of (*S*)-citronellol (**5**) to the allylated alcohol **9a** (*Scheme 2*), the α,β-unsaturated lactone **12** was efficiently accessed in preparation for stereocontrolled conjugate addition. The hydroxymethyl equivalent most suited to this task was (i-PrO)Me_2SiCH_2MgCl, which gave **13** predominantly in the presence of CuI and Me_3SiCl. Once the OH group was deprotected (→ **14**), it proved an easy matter to implement acid-catalyzed isomerization to lactone **15**, oxidation of which gave the pivotal aldehyde **16**. Condensation of **16** with $PhSeCH_2Li$ led *via* **21** to **22** (*Scheme 3*). Once the OH group was protected (→ **22b**), it proved possible to effect aldolization with crotonaldehyde (→ **23**). Exposure of **23** to acid gave the sub-target compound **25**. Its subsequent oxidation and thermal activation resulted in sequential selenoxide elimination with *Claisen* rearrangement (→ **26**). The structural features of **26** require that a chair-like transition state be adopted during the [3.3]sigmatropic event. With the clarification of these issues, a highly serviceable and more advanced assault on the crenulatans should prove capable of being mounted.

Introduction. – Extensive study by several groups in Japan [1], the United States [2], and Europe [3] has revealed brown algae of the genus *Dictyota* to be a particularly rich source of xenicane [4] and crenulatan diterpenes. In recent work, *Guella* and *Pietra* have shown that UV irradiation of (–)-4-hydroxydictyolactone (**1**) results in smooth photoisomerization to (+)-4-hydroxycrenulide (**2**) [5]. Consequently, as they concede, the probability is high that this conversion actually occurs under the influence of tropical sunlight acting on the seaweed at low tide.



1 **2**

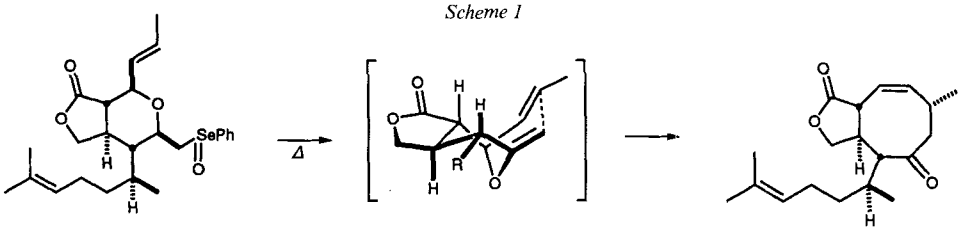
The interesting structural and configurational characteristics of the crenulatans are reflected in their central eight-membered ring [6], which features five stereogenic centers, and to which cyclopropane and butenolide (or equivalent) rings are fused. Although synthetic accomplishments in this area have been few [7], unique opportunities exist for

[1]) Procter and Gamble Fellow, 1990–1991.

the application of new and existing preparative methods. In the present paper, a general synthetic strategy is described wherein the stereogenicity inherent in the 6-methylhept-5-en-2-yl side chain is utilized as the point of reference for correlating the absolute configuration at the other relevant chiral centers.

Results and Discussion. – The focus of this study was to determine if *Claisen* rearrangements such as that associated with the isomerization of **3** would prove serviceable in providing the means for obtaining stereodefined cyclooct-4-enones (*Scheme 1*). At issue was whether the ponderal effect of the C_8 side chain would prove to be a deterrent to operation of the [3.3]-sigmatropic process *via* a requisite chair-like arrangement. This

Scheme 1



3 **4**

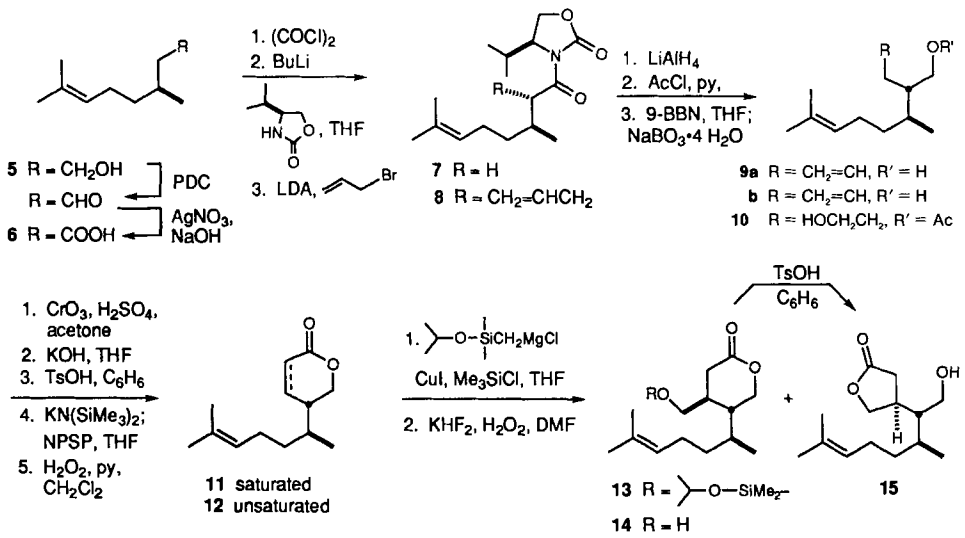
facet of the problem is somewhat simplified in **3**, since the C_8H_{15} side chain is projected equatorially during the electronic organization to give **4**. In future work, the consequences of orienting the R group axially (as ultimately required) are to be examined. Failure of either system to rearrange precisely as indicated would, of course, result in erosion of the capability to introduce a *cis* endocyclic double bond and provide an α-oriented secondary Me group.

In the selection of an optically active starting material for the synthesis at hand, the decision was made to take advantage of the existing chirality in (*S*)-citronellol (**5**). Since oxidations of **5** in acidic media are known to produce cyclic compounds rather than (*S*)-citronellic acid (**6**) as a consequence of the nearby presence of a highly reactive double bond, milder conditions are required to produce **6**. Although recourse to pyridinium dichromate (PDC) in DMF [8] works well on small scale, disadvantages arise during the processing of large amounts chiefly because of difficulties in workup. Much superior is a two-step sequence *via* (*S*)-citronellal in which the aldehyde produced by reaction with PDC in CH_2Cl_2 is oxidized with fresh silver oxide [9] (*Scheme 2*).

Having secured large quantities of **6**, we soon recognized that alkylation of its methyl ester with allyl bromide gave a 1:1 mixture of diastereoisomers. Consequently, the chiral center at the β-position is not capable of exerting diastereocontrol. Recourse was therefore made to (4*S*)-4-isopropyloxazolidin-2-one because of its predictable consequences on product configuration [10]. Indeed, when the lithium enolate of **7** was treated with allyl bromide at 0°, **8** was produced in isomerically pure condition (82%). The elevated reaction temperature was necessary to allow alkylation to proceed at a reasonable rate.

Following removal of the chiral auxiliary by $LiAH_4$ reduction, acetate **9b** was prepared and subjected to regioselective hydroboration with the bulky 9-BBN (9-borabicyclo[3.3.1]nonane) reagent. Mild *in situ* oxidation with sodium perborate [11] delivered hydroxy acetate **10** in 98% overall yield. The availability of **10** allowed access to be gained

Scheme 2



to lactone **11** *via* a one-pot three-step procedure consisting of *Jones* oxidation, saponification, and acid-catalyzed ring closure. Conversion of this intermediate to **12** was accomplished by means of organoselenium technology involving *N*-(phenylseleno)phthalimide (NPSP).

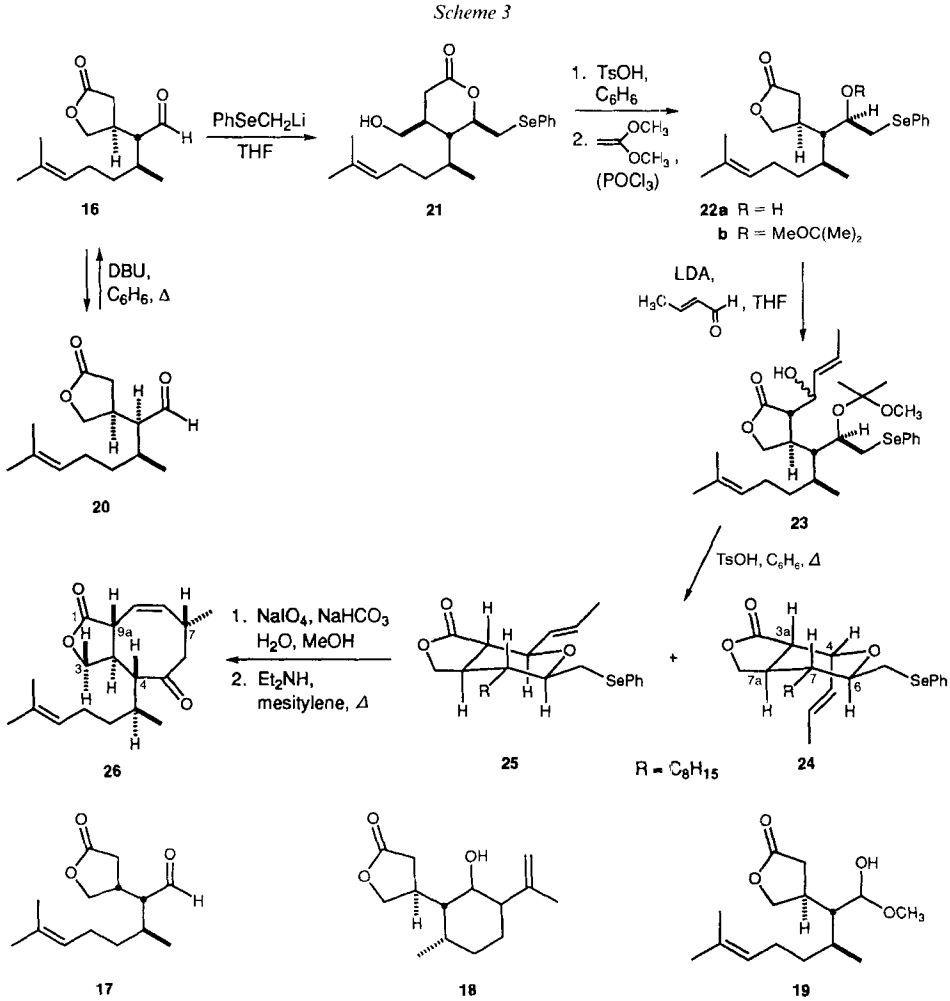
At this stage, the plan called for the introduction of a hydroxymethyl substituent in conjugate fashion to **12** [12]. When the cuprates derived from 4-MeO–$C_6H_4OCH_2Li$, 4-MeO–$C_6H_4CH_2OCH_2Li$, and $MeOCH_2OCH_2Li$ [13] were observed to add to **12** only in low yield, recourse was made alternatively to (i-PrO)Me_2SiCH_2MgCl and a catalytic quantity of CuI in the presence of Me_3SiCl [14]. Under the best conditions, which involved slow addition of the *Grignard* reagent to **12** admixed with the co-reagents at 0°, **13** was obtained in 76% yield with the β-isomer assumed to predominate heavily. The addition product proved to be very sensitive to acid, requiring that Et_3N be introduced prior to workup to absorb any HCl generated from hydrolysis of the remaining Me_3SiCl. Desilylation of **13** with KHF_2 and H_2O_2 in DMF [15] permitted exploration of the equilibration of **14** with **15**. Upon heating **14** with catalytic amounts of toluene-4-sulfonic acid in benzene, a mixture rich in **15** was produced, as expected on both thermodynamic and kinetic grounds [12]. The individual structural isomers were readily separated by chromatography on silica gel, at which point **14** was resubjected to the isomerization conditions. To safeguard structural integrity, **15** was invariably oxidized to **16** as soon as possible with PDC in the presence of powdered 3-Å molecular sieves.

The singular ease with which minor constituent **17** could be obtained (from **13**, after oxidation) free of its epimer prompted brief examination of the equilibration of aldehyde **16**. When **16** was exposed to trace quantities of toluene-4-sulfonic acid in benzene at room temperature, epimerization was not observed. Rather, an ene reaction took place rapidly to deliver homoallylic alcohol **18** in quantitative yield. Although the use of 4-chloroaniline in the mixed solvent system i-PrOH/AcOH 7:1 [16] provided an unknown

aromatic compound, and (lithium diisopropylamide) LDA proved to be totally destructive of **16**, mildly alkaline conditions such as K_2CO_3 in MeOH led to formation of the addition product **19**. Ultimately, heating **16** with 3 equiv. of DBU (1,8-diazabicyclo-[5.4.0]undec-7-ene) in benzene effected isomerization to **20**. At equilibrium, the two aldehydes **16** and **20** were present in a 1:1 ratio (*Scheme 3*). Unfortunately, unlike **16** and **17**, **16** and **26** proved to be chromatographically inseparable on a wide range of absorbents. As a consequence, designed epimerization should not be entertained here in the synthetic scheme, since the diastereoisomers exhibit inadequate physical differences to allow their isolation in pure form.

While initial efforts to achieve chemoselective 1,2-addition to the aldehyde C=O in **16** proved troublesome because of steric shielding, these difficulties could be circumvented by introducing $PhSeCH_2Li$ [17] under high-dilution conditions. The transient generation

Scheme 3



of a reactive alkoxide ion in this fashion resulted in kinetically controlled intramolecular attack at the lactone C=O to provide **21** as a single diastereoisomer in 90% yield. As a consequence of the lesser strain energy in **22**, efforts directed to the acid-catalyzed isomerization of **21** to **22** proved to work well and to shift the equilibrium well back in the direction of the five-ring lactone. Protection of the OH group in **22** permitted the direct aldol condensation of **22** with crotonaldehyde. On the basis of our past experiences, it was clear that the blocking group had to be introduced under acidic conditions to bypass reconversion to **21**. In addition, its ultimate removal under acidic conditions could also prove highly desirable since this transformation could be performed in tandem with the impending pyran-ring formation. For these reasons, **22** was treated with 2-methoxypropene in the presence of a catalytic amount of $POCl_3$ [18]. LDA proved adequately reactive as a promoter of the aldol process, this step delivering **23** as a 1:1 mixture of diastereoisomers in quantitative yield.

Upon heating **23** in benzene solution containing toluene-4-sulfonic acid, ring closure occurred to afford the bicyclic phenylseleno-substituted lactones **24** and **25** in 34 and 37% yield, respectively, after chromatographic separation. The stereoselectivity of these cyclizations is in agreement with the kinetically controlled ionization of the allylic OH group and with intramolecular capture of the cation on one of its two planar surfaces *via* a six-membered transition state. The specific reaction course dictates whether the propenyl substituent is projected axially as in **24** or equatorially as in **25**. The near-equal distribution of the two epimers suggested that ring closure occurred under kinetic control. In actuality, the cyclization was stereospecific since the two separated epimers of **23** cyclized cleanly in turn to **24** or to **25**. It would appear, therefore, that the surface from which the OH departs is sufficiently cluttered to invite nucleophilic attack from the backside direction. Lactones **24** and **25** could readily be distinguished on the basis of $^1H,^1H$ coupling constants exhibited by the protons residing on the tetrahydropyran ring (see *Exper. Part*, $J(3a,4) = 5$ Hz for **24** and 9.5 Hz for **25**). Also made evident by these spectral data was the fact that the $PhSeCH_2$ unit resides in an equatorial disposition. This finding formed the basis for the configurational assignment to this center in **21**–**25**. A further relevant point was the finding that **24** could indeed be converted into **25** upon being heated in benzene containing toluene-4-sulfonic acid. However, this process was very slow. After 1 week, only 50% of **24** had undergone isomerization. At longer reaction times, significant decomposition was observed; higher boiling solvents, *e.g.*, mesitylene, or stronger acids, *e.g.*, CF_3SO_3H, had the same effect only much more rapidly. No reaction occurred in more polar solvents such as 1,2-dimethoxyethane or when other possible catalysts, *e.g.*, $[Pd(PPh_3)_4]$, were present. Treatment with DBU resulted in epimerization at C(2).

Finally, **25** was oxidized to the selenoxide level with sodium periodate. Without purification, this intermediate was heated in mesitylene to bring about both the 1,2-elimination and *Claisen* rearrangement. Since this two-step process is mediated by a reactive vinyl ether, preservation of its integrity required that Et_2NH be present to neutralize the electrophilic PhSeOH liberated during its very formation. Under these conditions, **26** was obtained in 80% overall yield. The configurational assignments to **26** are soundly based on nuclear *Overhauser* experiments as indicated in the *Exper. Part*.

Consequently, the electronic reorganization association with this [3.3]-sigmatropic process unquestionably proceeds *via* the chair arrangement depicted in **3**. The transition-

state geometry guarantees the desired α-orientation of the ring Me group and the *cis*-configuration of the cyclooctenone double bond. Furthermore, the rearrangement occurs without adventitious epimerization at the two enolizable sites and without migration of the β,γ-unsaturated double bond into conjugation with the lactone C=O group.

The present achievements provide considerable insight into the requirements necessary for the actual adaptation of this scheme to the synthesis of crenulatan diterpenes of marine origin. The recent discovery [5] that the xenicane and crenulatan frameworks share in common a (*R*)-configurated stereocenter demands, of course, that (*R*)-citronellol be utilized at the outset. Beyond that, it is *not* just a matter of producing the (*R*,*R*)-isomer of **9a**, for this course of action will ultimately provide only the enantiomer of **26**, since the remaining stereocenters are introduced under the full control of those present in this alcohol. Consequently, a different stratagem is required to reach the proper diastereoisomer of **21** and of **25**. Once this essential matter is settled, there will remain the need for operation of the normal chair-like kinetic bias of the *Claisen* rearrangement as in **4** despite the axial orientation of the alkenyl chain R. We hope to be in a position to report on the outcome of these studies in due course.

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Experimental Part

General. M.p.: uncorrected. Solvents: reagent grade and in most cases dried before use. Column Chromatography (CC): *Woelm* silica gel (230–400 mesh) or *Merck Lobar* columns (*Lichroprep Si-60*); FC = flash chromatography. The purity of all compounds was shown to be ≥ 95% by TLC and high-field ^{1}H-NMR analyses. ^{1}H-NMR Spectra: at 300 MHz. ^{13}C-NMR Spectra: at 75 MHz unless otherwise noted. HR-MS: obtained at the Ohio State University Campus Chemical Instrumentation Center. Elemental analyses were performed at the Scandinavian Microanalytical Laboratory, Herlev, Denmark.

(S)-Citronellic Acid (= (S)-3,7-Dimethyloct-6-enoic Acid; **6**). To a well stirred suspension of **5** (48.32 g, 0.320 mmol) and dried, powdered 3 Å molecular sieves (150 g) in dry CH_2Cl_2 (500 ml) was added PDC (150 g, 0.399 mmol). The dark mixture was stirred at r.t. for 3 h before being diluted with Et_2O (1 l). The solid that was separated by filtration was extracted with Et_2O (2 × 250 ml), and the combined org. solns. were evaporated to give impure aldehyde.

A soln. of NaOH (51 g, 1.28 mol) in H_2O (220 ml) was treated dropwise with an aq. soln. (220 ml) of $AgNO_3$ (100 g, 0.588 mol). The brown silver oxide suspension was stirred vigorously for 30 min and the aldehyde was introduced dropwise. After overnight agitation, the insoluble solid was separated and washed with hot H_2O (2 × 30 ml). The combined aq. soln. was acidified and extracted with Et_2O (2 × 500 ml) and the org. phase dried and evaporated: 40.0 g (76%) of pure **6** [8].

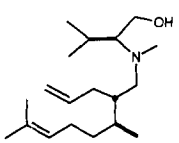
(4S)-3-[(3S)-3,7-Dimethyloct-6-enoyl]-4-isopropyloxazolidin-2-one (**7**). To a soln. of **6** (58.46 g, 0.344 mol) in 280 ml of dry benzene and 110 ml of 2-methylbut-2-ene was added oxalyl chloride (33.74 ml, 0.380 mol). The light yellow soln. was stirred at r.t. for 2 h before being evaporated to give the crude acyl chloride as a yellow liquid. To a cold (−78°) soln. of (4*S*)-4-isopropyloxazolidin-2-one (48.5 g, 0.363 mol) in 2 l of dry THF was added dropwise 1.5M BuLi in hexane (251.3 ml, 0.377 mol) during 0.5 h before the above acyl chloride was introduced *via* cannula. The mixture was stirred at −78° for 3 h before being quenched with sat. NH_4Cl soln. (250 ml). The aq. soln. was extracted with Et_2O (2 × 250 ml), the combined org. phase dried and evaporated, and the yellow residue chromatographed (silica gel, 30% Et_2O/petroleum ether): 93.33 g (97%) of **7**. Colorless liquid. $[\alpha]_D^{20} = +58.2$ ($c = 0.95$, $CHCl_3$). IR (neat): 1780, 1700, 1380, 1200. ^{1}H-NMR ($CDCl_3$): 5.10 (*m*, 1 H); 4.44 (*m*, 1 H); 4.22 (*m*, 2 H); 3.02 (*dd*, $J = 15.9, 5.5$, 1 H); 2.68 (*dd*, $J = 15.9, 8.2$, 1 H); 2.37 (*m*, 1 H); 2.03 (*m*, 3 H); 1.68 (*s*, 3 H); 1.60 (*s*, 3 H); 1.42 (*m*, 1 H); 1.27 (*m*, 1 H); 0.95 (*d*, $J = 6.7$, 3 H); 0.91 (*d*, $J = 7.0$, 3 H); 0.97 (*d*, $J = 7.0$, 3 H). ^{13}C-NMR ($CDCl_3$): 172.8, 154.0, 131.4, 124.4, 63.2, 58.4, 42.4, 36.9, 29.5, 28.4, 25.7, 25.4, 19.5, 18.0, 17.6, 14.6. MS: 281.1978 (M^+, calc. 281.1991). Anal. calc. for $C_{16}H_{27}NO_3$: C 68.29, H 9.67; found: C 68.52, H 9.69.

(4S)-3-[(2S,3S)-2-Allyl-3,7-dimethyloct-6-enoyl]-4-isopropyloxazolidin-2-one (**8**). To a cold (−78°) LDA (lithium diisopropylamide) soln. prepared from i-Pr_2NH (51.4 ml, 0.367 mol) and 1.5M BuLi in hexanes (230 ml, 0.345 mol) in 600 ml of dry THF was added dropwise within 1 h a soln. of **7** (93.33 g, 0.332 mol) in 200 ml of dry THF. The light yellow-brown soln. was vigorously stirred at −78° for 3 h and warmed to 0° during 30 min at which point allyl bromide (86.2 ml, 0.996 mol) was added *via* syringe. The mixture was stirred at 0° overnight, cooled to −78°, and quenched with sat. NH_4Cl soln. (100 ml). The resulting orange soln. was poured into 400 ml of ice-cold 1N HCl and extracted with Et_2O (2 × 300 ml). The combined org. phase was dried and evaporated and the residue purified by CC (silica gel, 20% Et_2O/petroleum ether): 76.95 g (72%) of **8** and 11.3 g (12%) of recovered **7**. Overall yield of **8** 82%. Colorless liquid. $[\alpha]_D^{20} = +66.6$ ($c = 0.65$, $CHCl_3$). IR (neat): 1770, 1690, 1380, 1200. ^{1}H-NMR (200 MHz, $CDCl_3$): 5.86–5.66 (series of *m*, 1 H); 5.08–4.76 (series of *m*, 3 H); 4.45 (*m*, 1 H); 4.18 (*m*, 2 H); 3.97 (*m*, 1 H); 2.51–2.25 (series of *m*, 3 H); 2.10–1.72 (series of *m*, 3 H); 1.66 (*s*, 3 H); 1.58 (*s*, 3 H); 1.48 (*m*, 1 H); 1.16 (*m*, 1 H); 0.93 (*d*, $J = 6.8$, 3 H); 0.88 (*d*, $J = 7.1$, 3 H); 0.83 (*d*, $J = 6.9$, 3 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 175.6, 153.8, 135.6, 131.5, 124.2, 116.7, 62.8, 58.7, 47.0, 34.7, 33.9, 32.9, 28.2, 25.7, 25.2, 18.0, 17.6, 17.1, 14.5. MS: 321.2341 (M^+, calc. 321.2304). Anal. calc. for $C_{19}H_{31}NO_3$: C 70.99, H 9.72; found: C 71.10, H 9.80.

(2S,3S)-2-Allyl-3,7-dimethyloct-6-enol (**9a**). To **8** (8.03 g, 0.0250 mol) in 1.25 l of dry Et_2O at −78°, $LiAlH_4$ (2.85 g, 0.0750 mol) was added at once, and the gray suspension was stirred vigorously as the temp. was raised from −78° to 20° within 2 h and at r.t. overnight. H_2O (4 ml) was added at 0° to carefully destroy the excess hydride, followed by 2M NaOH (4 ml) and H_2O (10 ml). After filtration of solid, the Et_2O filtrate was washed with 2M H_2SO_4 (100 ml), dried, and evaporated and the residue chromatographed (silica gel, 30% Et_2O/petroleum ether): 3.68 g (75%) of **9a**. The acid aq. soln. was neutralized with 2N NaOH and extracted with Et_2O (2 × 100 ml). Evaporation of the dried Et_2O soln. gave 2.0 g (25%) of *(2S)-2-{N-[(2S,3S)-2-allyl-3,7-dimethyloct-6-enyl]-N-methylamino}-3-methylbutanol* **27**.

9a: Colorless liquid. $[\alpha]_D^{20} = -10.1$ ($c = 1.60$, $CHCl_3$). IR (neat): 3340, 1440, 1380, 1040, 910. ^{1}H-NMR ($CDCl_3$): 5.83 (*dddd*, $J = 15.6$, 10.0, 7.1, 2.9, 1 H); 5.13–4.98 (series of *m*, 3 H); 3.65 (*dd*, $J = 10.8$, 5.1, 1 H); 3.55 (*dd*, $J = 10.8$, 6.5, 1 H); 2.13 (*tt*, $J = 17.0$, 1.3, 2 H); 2.03 (*m*, 1 H); 1.93 (*m*, 1 H); 1.68 (*d*, $J = 1.1$, 3 H); 1.60 (*s*, 3 H); 1.66–1.50 (series of *m*, 2 H); 1.43 (*m*, 1 H); 1.33 (br. *s*, 1 H); 1.19 (*m*, 1 H); 0.88 (*d*, $J = 6.8$, 3 H). ^{13}C-NMR ($CDCl_3$): 138.2, 131.4, 126.7, 115.8, 63.6, 45.3, 34.1, 33.8, 33.0, 26.0, 25.7, 17.7, 16.1. MS: 196.1807 (M^+, calc. 196.1827). Anal. calc. for $C_{13}H_{24}O$: C 79.53, H 12.32; found: C 79.12, H 12.40.

27: Colorless liquid. $[\alpha]_D^{20} = -0.45$ ($c = 1.32$, $CHCl_3$). IR (neat): 3450, 1440, 1370, 1070, 1050, 910. ^{1}H-NMR (200 MHz, $CDCl_3$): 5.74 (*dddd*, $J = 14.0$, 10.1, 7.0, 3.0, 1 H); 5.13–4.94 (series of *m*, 3 H); 3.53 (*dd*, $J = 10.3$, 5.0, 2 H); 3.19 (*t*, $J = 10$,4, 1 H); 2.55 (*dd*, $J = 13.0$, 5.9, 1 H); 2.42 (*dd*, $J = 13.0$, 7.5, 1 H); 2.38–2.21 (series of *m*, 1 H); 2.29 (*s*, 3 H); 2.02 (*t*, $J = 6.9$, 2 H); 1.96–1.74 (series of *m*, 3 H); 1.67 (*s*, 3 H); 1.63–1.51 (series of *m*, 2 H); 1.59 (*s*, 3 H); 1.40–1.23 (series of *m*, 1 H); 1.21–1.04 (series of *m*, 1 H); 0.99 (*d*, $J = 6.7$, 3 H); 0.83 (*d*, $J = 6.8$, 3 H); 0.81 (*d*, $J = 6.7$, 3 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 138.1, 131.3, 124.7, 115.5, 70.6, 59.5, 55.7, 44.3, 36.9, 34.1, 33.4, 32.6, 27.5, 26.2, 25.7, 22.6, 19.9, 17.6, 15.8. MS: 295.2877 (M^+, calc. 295.2875). Anal. calc. for $C_{19}H_{37}NO$: C 77.23, H 12.62; found: C 77.27, H 12.68.



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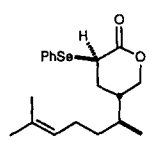

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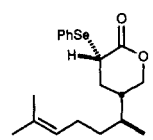

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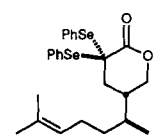

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(2S,3S)-2-Allyl-3,7-dimethyloct-6-en-1-yl Acetate (**9b**). Four lots of 13.12 g (40.9 mmol) of **8** were reduced with $LiAlH_4$ (4.66 g, 0.123 mol) in the predescribed manner, and the reaction mixtures were combined for workup. The crude alcohol so produced, 4-(dimethylamino)pyridine (0.3 g), and pyridine (66.3 ml, 0.820 mol) in 400 ml of CH_2Cl_2 were cooled to −20° and treated with acetyl chloride (35 ml, 0.49 mol) over 10 min. The white suspension was stirred while being allowed to warm to r.t. during 1 h, and at r.t. for 4 h. After being cooled to 0°, the brown suspension was washed with 10% HCl (100 ml) and sat. $NaHCO_3$ soln. (100 ml), dried, and evaporated. The residue was purified by CC (silica gel, 5% Et_2O/petroleum ether): 27.7 g (71%) of **9b**. Colorless liquid. $[\alpha]_D^{20} = +4.3$ ($c = 0.44$, $CHCl_3$). IR (neat): 1720, 1230. ^{1}H-NMR (250 MHz, $CDCl_3$): 5.73 (*m*, 1 H); 5.11–4.98 (series of *m*, 3 H); 4.06 (*dd*, $J = 11.1$, 5.8, 1 H); 3.95 (*dd*, $J = 11.2$, 6.6, 1 H); 2.09 (*t*, $J = 7.0$, 2 H); 2.03 (*s*, 3 H); 1.97 (*m*, 3 H); 1.74 (*m*, 1 H); 1.68 (*s*, 3 H); 1.60 (*s*, 3 H); 1.39 (*m*, 1 H); 1.19 (*m*, 1 H); 0.86 (*d*, $J = 6.8$, 3 H). ^{13}C-NMR (62.5 MHz, $CDCl_3$):

171.1, 137.1, 131.4, 124.5, 116.1, 64.9, 41.5, 34.2, 33.7, 32.9, 25.9, 25.6, 21.0, 17.6, 15.6. MS: 178.1698 (M^+, calc. 178.1721). Anal. calc. for $C_{15}H_{26}O_3$: C 75.58, H 10.99; found: C 75.28, H 10.87.

(2S,3S)-2-(3-Hydroxypropyl)-3,7-dimethyloct-6-enyl Acetate (**10**). To a well-stirred soln. of **9b** (27.7 g, 0.117 mol) in 220 ml of dry THF was added a soln. of 0.5M 9-BBN in THF (280 ml, 0.140 mol) *via* syringe over 10 min. The mixture was vigorously stirred for 7 h, then quenched with 150 ml of H_2O. Sodium perborate hydrate (66.5 g, 0.433 mol) was added to the cloudy soln., and the suspension was vigorously stirred overnight. The aq. soln. was extracted with Et_2O (2 × 300 ml), the combined org. phase dried and evaporated, and the residue chromatographed (silica gel, 5% MeOH/CH_2Cl_2): 29.32 g (98%) of **10**. Colorless oil. $[\alpha]_D^{20} = -1.4$ ($c = 1.55$, $CHCl_3$). IR (neat): 3400, 1730, 1230. ^{1}H-NMR (250 MHz, $CDCl_3$): 5.04 (*m*, 1 H); 4.02 (*td*, $J = 11.1$, 5.4, 1 H); 3.92 (*dd*, $J = 11.1$, 6.3, 1 H); 3.58 (*t*, $J = 6.5$, 2 H); 2.00 (*s*, 3 H); 1.95 (*m*, 2 H); 1.64 (*s*, 3 H); 1.56 (*s*, 3 H); 1.60–1.42 (series of *m*, 5 H); 1.35 (*m*, 3 H); 1.18 (*m*, 1 H); 0.83 (*d*, $J = 6.8$, 3 H). ^{13}C-NMR (62.5 MHz, $CDCl_3$): 171.2, 131.3, 124.5, 65.3, 62.8, 41.5, 34.1, 33.3, 30.7, 25.9, 25.6, 25.3, 20.9, 17.5, 15.6. MS: 241.1823 (M^+, calc. 241.1804).

*(5S)-5-[(1S)-1,5-Dimethylhex-4-enyl]tetrahydro-2*H*-pyran-2-one* (**11**). To a brown soln. of CrO_3 (39.6 g, 0.396 mol) and 1.5M H_2SO_4 (620 ml, 0.931 mol) in 100 ml of acetone was added within 40 min a soln. of **10** (26.8 g, 0.105 mol) in 1 l of acetone at 0°. The resulting black mixture was stirred vigorously for 3 h, quenched with i-PrOH (40 ml), and filtered through a pad of *Celite*. The *Celite* was washed with acetone (2 × 500 ml). The filtrate was concentrated under vacuum to remove volatile compounds and treated with a soln. of KOH (56 g, 1.0 mol) in 100 ml of H_2O at 0°. This mixture was vigorously stirred overnight. After acidification at 0° with conc. HCl soln., the soln. was extracted with Et_2O (3 × 500 ml). The combined Et_2O phase was dried and evaporated and the residue dissolved in 1.5 l of benzene, treated with $TsOH \cdot H_2O$ (0.2 g), and refluxed for 4 h under a *Dean-Stark* trap. The brown soln. was washed with sat. $NaHCO_3$ soln. (100 ml), dried, and evaporated. The yellow residue was purified by CC (silica gel, 15% Et_2O/petroleum ether): 10.22 g (4%) of **11**. Colorless liquid. $[\alpha]_D^{20} = -16.2$ ($c = 0.60$, $CHCl_3$). IR (neat): 1745. ^{1}H-NMR (250 MHz, $CDCl_3$): 5.06 (*dd*, $J = 7.0$, 5.7, 1 H); 4.33 (*ddd*, $J = 11.0$, 4.5, 1.6, 1 H); 4.07 (*dd*, $J = 10.7$, 10.3, 1 H); 2.67–2.40 (series of *m*, 2 H); 2.07–1.88 (series of *m*, 3 H); 1.85–1.56 (series of *m*, 2 H); 1.68 (*s*, 3 H); 1.60 (*s*, 3 H); 1.52–1.33 (series of *m*, 2 H); 1.25–1.10 (series of *m*, 1 H); 0.92 (*d*, $J = 6.7$, 3 H). ^{13}C-NMR (20 MHz, $CDCl_3$): 171.8, 131.9, 124.0, 71.5, 37.8, 34.0, 33.9, 29.4, 25.6, 25.4, 23.1, 17.7, 16.2. MS: 210.1629 (M^+, calc. 210.1620). Anal. calc. for $C_{13}H_{22}O_2$: C 74.24, H 10.54; found: C 74.09, H 10.52.

*(3R,5S)- and (3S,5S)-5-[(1S)-1,5-Dimethylhex-4-enyl]tetrahydro-3-(phenylseleno)-2*H*-pyran-2-one* (**28** and **29**, resp.). To 0.5M potassium hexamethyldisilazide in toluene (62.9 ml, 0.0315 mol) dissolved in 100 ml of THF at −78° was added dropwise within 10 min a soln. of **11** (3.00 g, 0.0143 mol) in 25 ml of THF. The mixture was stirred at −78° for 1.5 h before solid *N*-(phenylseleno)phthalimide (NPSP; 4.97 g, 0.0164 mol) was added in one portion. The white suspension was stirred at −78° for 1 h before being warmed to 20° during 2 h, maintained at r.t. for 1 h, and poured into a mixture of 100 ml of Et_2O and 100 ml of H_2O. The aq. phase was extracted with Et_2O (100 ml), the combined org. phase dried and evaporated, and the residue chromatographed (silica gel, 10% Et_2O/petroleum ether): 4.22 g (81%) of **28** and **29** as well as 0.24 g (8%) of recovered **11**. Yield 88% based on unconsumed **11**. When 1 equiv. of base was used, *(5S)-5-[(1S)-1,5-dimethylhex-4-enyl]-tetrahydro-3,3-bis-(phenylseleno)-2*H*-pyran-2-one* (**30**) was also isolated in small amounts.

28: Yellow oil. $[\alpha]_D^{20} = -49.1$ ($c = 1.00$, $CHCl_3$). IR (neat): 1730, 1475, 1190. ^{1}H-NMR (250 MHz, $CDCl_3$): 7.63 (*m*, 2 H); 7.29 (*m*, 3 H); 5.01 (*m*, 1 H); 4.26 (*dd*, $J = 11.0$, 4.4, 1 H); 4.09 (*dd*, $J = 11.0$, 10.3, 1 H); 3.95 (*dd*, $J = 9.0$, 8.1, 1 H); 2.33 (*m*, 1 H); 2.01–1.70 (series of *m*, 4 H); 1.65 (*s*, 3 H); 1.56 (*s*, 3 H); 1.46–1.21 (series of *m*, 2 H); 1.20–1.05 (series of *m*, 1 H); 0.84 (*d*, $J = 6.8$ Hz, 3 H). ^{13}C-NMR (20 MHz, $CDCl_3$): 170.6, 135.2, 131.9, 129.2, 128.8, 127.8, 123.8, 70.8, 38.6, 37.8, 34.2, 33.8, 31.6, 25.6, 25.3, 17.6, 16.0. MS: 366.1158 (M^+, calc. 366.1097).

29: Yellow oil. $[\alpha]_D^{20} = -3.2$ ($c = 0.74$, $CHCl_3$). IR (neat): 1740, 1385, 1440, 1230, 1190, 1090. ^{1}H-NMR ($CDCl_3$): 7.68–7.65 (*m*, 2 H); 7.35–7.28 (*m*, 3 H); 5.04 (*m*, 1 H); 4.44 (*ddd*, $J = 11.4$, 5.0, 1.7, 1 H); 4.11 (*d*, $J = 11.2$, 1 H); 4.04 (*dd*, $J = 4.0$, 5.4, 1 H); 2.19–1.97 (series of *m*, 4 H); 1.90 (*m*, 1 H); 1.69 (*d*, $J = 1.0$, 3 H); 1.60 (*s*, 3 H); 1.46–1.32 (series of *m*, 2 H); 1.20 (*m*, 1 H); 0.89 (*d*, $J = 6.8$, 3 H). ^{13}C-NMR ($CDCl_3$): 170.6, 135.4, 132.0, 129.3, 128.7, 128.3, 123.9, 71.9, 39.4, 35.3, 33.8, 33.7, 31.2, 25.7, 25.2, 17.7, 16.1. MS: 366.1079 (M^+, calc. 366.1097).

30: Yellow oil. $[\alpha]_D^{20} = -127.1$ ($c = 0.70$, $CHCl_3$). IR (neat): 1720, 1175, 1125. ^{1}H-NMR (250 MHz, $CDCl_3$): 7.77–7.67 (series of *m*, 4 H); 7.49–7.30 (series of *m*, 6 H); 4.95 (*m*, 1 H); 4.29 (*m*, 1 H); 3.78 (*m*, 1 H); 2.14–1.77 (series of *m*, 4 H); 1.68 (*d*, $J = 0.9$, 3 H); 1.56 (*s*, 3 H); 1.26, 1.01 (series of *m*, 2 H); 0.99–0.85 (series of *m*, 2 H); 0.69 (*d*, $J = 6.8$, 3 H). ^{13}C-NMR (62.5 MHz, $CDCl_3$): 169.6, 137.7, 137.0, 131.9, 130.0, 129.6, 129.09, 129.05, 127.9, 123.8, 72.4, 49.0, 38.7, 36.3, 33.7, 33.5, 25.6, 25.2, 17.6, 15.9. MS: 522.0570 (M^+, calc. 522.0576).

*(5S)-5-[(1S)-1,5-Dimethylhex-4-enyl]-5,6-dihydro-2*H*-pyran-2-one* (**12**). To a well stirred soln. of **29** and **30** (4.53 g, 0.0124 mmol) in 150 ml CH_2Cl_2 and 3.0 ml (0.0372 mmol) of pyridine was added dropwise a soln. of 30% H_2O_2 (2.97 ml, 0.0262 mmol) in 3 ml of H_2O at 0°. The mixture was stirred at 0° for 30 min before being quenched with 7% $NaHCO_3$ soln. (100 ml) and extracted with CH_2Cl_2 (2 × 100 ml). The combined org. phase was dried and

evaporated and the residue chromatographed (silica gel, 50% Et_2O/petroleum ether): 2.15 g (83%) of **12**. Colorless liquid. $[\alpha]_D^{20} = -116.6$ ($c = 0.79$, $CHCl_3$). IR (neat): 1740, 1240, 1080, 830. ^{1}H-NMR ($CDCl_3$): 6.84 (*dd*, $J = 9.9$, 3.9, 1 H); 6.00 (*dd*, $J = 9.9$, 2.0, 1 H); 5.04 (*m*, 1 H); 4.38 (*ddd*, $J = 11.3$, 5.3, 0.8, 1 H); 4.27 (*dd*, $J = 11.2$, 7.2, 1 H); 2.41 (*m*, 1 H); 2.06–1.90 (series of *m*, 2 H); 1.76–1.68 (series of *m*, 1 H); 1.66 (*d*, $J = 1.0$, 3 H); 1.58 (*s*, 3 H); 1.50–1.39 (series of *m*, 1 H); 1.30–1.18 (series of *m*, 1 H); 0.95 (*d*, $J = 6.9$, 3 H). ^{13}C-NMR ($CDCl_3$): 163.8, 149.6, 132.1, 123.6, 120.9, 68.5, 38.6, 33.9, 33.80, 25.6, 25.4, 17.6, 16.3. MS: 208.1476 (M^+, calc. 208.1464). Anal. calc. for $C_{13}H_{20}O_2$: C 74.96, H 9.68; found: C 75.04, H 9.80.

*(4*S*,5*R*)-5-[(1*S*)-1,5-Dimethylhex-4-enyl]tetrahydro-4-{[(isopropoxy)dimethylsilyloxy]methyl}-2*H*-pyran-2-one* (**13**). To a refluxing suspension of Mg turnings (2.43 g, 0.10 mol) in 100 ml of THF was added CH_2Br_2 (10 drops) and (chloromethyl)dimethyl(isopropoxy)silane (10 ml, 0.10 mol) over 10 min. The suspension was refluxed for 1.5 h to form a black-green soln. which was cannulated into a 100-ml flask to remove small particles of Mg turnings and stored under N_2. A soln. of **12** (1.13 g, 0.00543 mol) in 100 ml of dry THF was treated with CuI (103 mg, 0.541 mmol) and Me_3SiCl (2.0 ml, 0.0159 mmol) at 0°. To the suspension at 0° was added dropwise within 30 min a 1.0M soln. of the *Grignard* reagent (6.7 ml, 0.0067 mol). The light yellow soln. was stirred at 0° for 1 h before 5 ml of Et_3N were introduced, followed by H_2O (50 ml). The aq. soln. was extracted with Et_2O (3 × 100 ml), the combined org. extract dried and evaporated, and the residue subjected to MPLC (30% Et_2O/petroleum ether): 1.4 g (76%) of **13**. Colorless liquid. $[\alpha]_D^{20} = +10.8$ ($c = 0.66$, $CHCl_3$). IR (neat): 1750, 1030, 880. ^{1}H-NMR ($CDCl_3$): 5.07 (*m*, 1 H); 4.24 (*dd*, $J = 11.5$, 5.0, 1 H); 4.09 (*dd*, $J = 11.5$, 8.2, 1 H); 3.99 (*sept.*, $J = 6.1$ Hz, 1 H); 2.73 (*dd*, $J = 16.2$, 6.4, 1 H); 2.28 (*dd*, $J = 16.2$, 8.0, 1 H); 2.25–1.71 (series of *m*, 3 H); 1.68 (*s*, 3 H); 1.60 (*s*, 3 H); 1.56 (*m*, 1 H); 1.42–1.22 (series of *m*, 3 H); 1.14 (*d*, $J = 6.1$, 6 H); 0.86 (*d*, $J = 6.9$, 3 H); 0.61 (*m*, 1 H); 0.14 (*s*, 6 H); 0.10 (*m*, 1 H). ^{13}C-NMR (62.5 MHz, $CDCl_3$): 172.7, 131.9, 124.0, 68.1, 65.2, 45.9, 37.3, 35.1, 30.3, 25.9, 25.8 (2 C), 25.7, 24.4, 17.7, 14.8, −0.4, −0.6. MS: 340.2462 (M^+, calc. 340.2434).

*(4*S*,5*R*)-5-[(1*S*)-1,5-Dimethylhex-4-enyl]tetrahydro-4-(hydroxymethyl)-2*H*-pyran-2-one* (**14**) *and (4*S*)-4,5-Dihydro-4-[(1*R*,2*S*)-1-(hydroxymethyl)-2,6-dimethylhept-5-enyl]furan-2(3*H*)-one* (**15**). To a soln. of **13** (1.0 g, 2.9 mmol) in DMF (50 ml) was added successively KHF_2 (460 mg, 5.9 mmol) and 30% H_2O_2 soln. (4 ml, 35 mmol). The resulting mixture was heated to 60° with vigorous stirring for 4 h to generate a colorless soln. which was cooled to 20°, diluted with Et_2O (200 ml), and washed with sat. NH_4Cl soln. (100 ml). The aq. phase was acidified with HCl to pH 1 and extracted with Et_2O (5 × 100 ml). The combined org. layer was washed in turn with 10% $NaHSO_3$ soln. (200 ml) and H_2O (200 ml), dried, and evaporated: 730 mg of yellow oil. This material was divided into two 365-mg batches, each of which was diluted with benzene (150 ml) and refluxed under N_2 in the presence of toluene-4-sulfonic acid (11 mg, 4 mol-%) for 1 h. The cooled mixture was treated with four drops of pyridine, evaporated, and subjected to MPLC (silica gel, Et_2O) to provide **14** (110 mg) and **15** (95 mg).

Lactone **15** was immediately taken up in dry CH_2Cl_2 (60 ml), stirred vigorously with 4-Å molecular sieves (210 mg) and PDC (210 mg, 0.56 mmol) for 1.5 h, and diluted with Et_2O (200 ml). This soln. was filtered through a thick pad of 4-Å sieves and evaporated: 86 mg of pure *(α*R*,3*S*)-α-[(1*S*)-1,5-dimethylhex-4-enyl]-tetrahydro-5-oxofuran-3-acetaldehyde* (**16**).

Lactone **14** was resubjected to the original isomerization conditions. In this way, 1 g of **13** provided 250 mg (36% overall) of **16**.

Depending on the purity of **13**, small quantities of the epimeric *(α*R*,3*R*)-α-[(1*S*)-1,5-dimethylhex-4-enyl]-tetrahydro-5-oxofuran-3-acetaldehyde* (**17**) were obtained.

14: Colorless oil. IR (neat): 3400, 1740. ^{1}H-NMR ($CDCl_3$): 5.07 (*m*, 1 H); 4.23 (*dd*, $J = 11.5$, 5.0, 1 H); 4.12 (*dd*, $J = 11.5$, 8.3, 1 H); 3.66 (*dd*, $J = 10.6$, 4.4, 1 H); 3.53 (*dd*, $J = 10.6$, 6.6, 1 H); 2.57 (*d*, $J = 6.6$, 2 H); 2.11–1.95 (series of *m*, 3 H); 1.69 (*s*, 3 H); 1.61 (*s*, 3 H); 1.43 (*m*, 2 H); 1.34–1.21 (series of *m*, 2 H); 1.23 (br. *s*, 1 H); 0.93 (*d*, $J = 6.8$, 3 H). ^{13}C-NMR ($CDCl_3$): 173.3, 132.1, 123.9, 67.9, 65.5, 39.2, 36.5, 34.7, 33.9, 31.8, 25.8, 17.7, 15.6. MS: 222.1632 ($[M - H_2O]^+$, calc. 222.1619).

15: Colorless oil. IR (neat): 1780. ^{1}H-NMR ($CDCl_3$): 5.07 (*m*, 1 H); 4.43 (*m*, 1 H); 3.97 (*m*, 1 H); 3.76 (*dd*, $J = 10.7$, 4.6, 1 H); 3.67 (*m*, 1 H); 2.76–2.56 (series of *m*, 2 H); 2.46 (*m*, 1 H); 2.01 (*m*, 2 H); 1.70 (*d*, $J = 4.5$, 3 H); 1.62 (*d*, $J = 4.5$, 3 H); 1.52–1.34 (series of *m*, 4 H); 1.27 (br. *s*, 1 H); 0.90 (*d*, $J = 6.5$, 3 H). ^{13}C-NMR ($CDCl_3$): 177.5, 132.0, 124.0, 72.6, 61.9, 47.5, 37.1, 35.3, 33.7, 32.7, 26.0, 25.7, 17.7, 15.6. MS: 222.1613 ($[M - H_2O]^+$, calc. 222.1619).

16: Colorless oil. $[\alpha]_D^{20} = -32.7$ ($c = 1.8$, $CHCl_3$). IR ($CHCl_3$): 1740, 1730. ^{1}H-NMR ($CDCl_3$): 9.78 (*d*, $J = 1.8$, 1 H); 5.08 (*m*, 1 H); 4.42 (*dd*, $J = 7.8$, 9.0, 1 H); 3.94 (*t*, $J = 9.0$, 1 H); 2.95 (*m*, 1 H); 2.78 (*dd*, $J = 8.3$, 17.1, 1 H); 2.48 (*ddd*, $J = 1.8$, 3.8, 10.0, 1 H); 2.14 (*dd*, $J = 9.9$, 17.5, 1 H); 2.15–1.95 (*m*, 2 H); 1.70 (*d*, $J = 1.0$, 3 H); 1.62 (*s*, 3 H); 1.52–1.35 (series of *m*, 3 H); 0.97 (*d*, $J = 7.0$, 3 H). ^{13}C-NMR ($CDCl_3$): 202.8, 176.3, 132.6, 123.1, 70.9, 58.8, 35.2, 33.4, 33.1, 32.5, 25.7, 25.6, 17.7, 15.8. MS: 238.1568 (M^+, calc. 238.1568).

17: Colorless liquid. $[\alpha]_D^{20} = -17.5$ ($c = 1.5$, $CHCl_3$). IR ($CHCl_3$): 1750, 1730. ^{1}H-NMR ($CDCl_3$): 9.75 (*d*, $J = 1.7$, 1 H); 5.04 (*m*, 1 H); 2.41 (*ddd*, $J = 1.7, 3.7, 10.1$, 1 H); 2.18 (*dd*, $J = 10.4, 17.3$, 1 H); 2.15–1.87 (series of *m*, 2 H); 1.69 (*s*, 3 H); 1.60 (*s*, 3 H); 1.55–1.32 (series of *m*, 3 H); 1.11 (*d*, $J = 7.0$, 3 H). ^{13}C-NMR ($CDCl_3$): 202.4, 176.2, 132.8, 123.1, 71.1, 60.0, 33.3, 33.2, 33.0, 31.9, 25.72, 25.68, 17.8, 17.1. MS: 239.1638 ($[M + H]^+$, calc. 239.1647).

Conversion of **16** *to* **18–20**. A soln. of **16** (5.8 mg, 0.024 mmol) in dry benzene (3 ml) was treated with a crystal of toluene-4-sulfonic acid, stirred at r.t. for 3 h, washed with H_2O, dried, and evaporated: 5.7 mg (98%) of *(4S)-4,5-dihydro-4-[(1R,6S)-2-hydroxy-3-isopropenyl-6-methylcyclohexyl]furan-2(3H)-one* (**18**). Colorless oil. IR ($CHCl_3$): 2900, 1780. ^{1}H-NMR ($CDCl_3$): 5.01 (*s*, 1 H); 4.84 (*s*, 1 H); 4.48 (*t*, $J = 8.1$, 1 H); 3.94 (*t*, $J = 8.1$, 1 H); 3.75 (*s*, 1 H); 3.14–3.04 (*m*, 1 H); 2.70 (*dd*, $J = 8.1, 17.0$, 1 H); 2.26 (*dd*, $J = 11.0, 17.0$, 1 H); 2.00 (*d*, $J = 12.4$, 1 H); 1.92–1.70 (*m*, 1 H); 1.79 (*s*, 3 H); 1.62–1.48 (*m*, 4 H); 1.47–1.30 (*m*, 2 H); 1.10 (*d*, $J = 7.3$, 3 H). MS: 238.1549 (M^+, calc. 238.1569).

A soln. of **16** (10.7 mg, 0.045 mmol) in MeOH (2 ml) was treated with K_2CO_3 (6 mg, 0.045 mmol), stirred at r.t. for 40 min, diluted with CH_2Cl_2, washed with sat. NH_4Cl soln. (3 × 10 ml), dried, and evaporated: 10.3 mg (85%) of *(αR,3S)-α-[(1S)-1,5-dimethylhex-4-enyl]tetrahydro-5-oxafuran-3-acetaldehyde 3-(methyl hemiacetal)* (**19**). Colorless oil. IR ($CHCl_3$): 1760. ^{1}H-NMR ($CDCl_3$): 5.24 (br. *m*, 1 H); 5.10 (br. *t*, $J = 7.1$, 1 H); 4.16 (*t*, $J = 8.4$, 1 H); 3.75 (*t*, $J = 8.4$, 1 H); 3.68 (*s*, 3 H); 2.64 (*dd*, $J = 4.7, 16$, 1 H); 2.50 (*dd*, $J = 9.1, 1.6$, 1 H); 2.15–1.85 (*m*, 3 H); 1.85–1.73 (*m*, 1 H); 1.68 (*s*, 3 H); 1.60 (*s*, 3 H); 1.50–1.30 (*m*, 1 H); 1.25–1.10 (*m*, 1 H); 1.25–1.10 (*m*, 3 H); 0.93 (*d*, $J = 6.7$, 3 H). MS: 270.1833 (M^+, calc. 270.1831).

A soln. of **16** (11.5 mg, 0.048 mmol) in dry benzene (1 ml) was treated with DBU (22 µl, 0.15 mmol), refluxed for 48 h, cooled to 20°, diluted with CH_2Cl_2, washed with NH_4Cl soln., dried, and evaporated: 10 mg (87%) of **16**/**20** 1:1. Although these epimers could not be chromatographically separated, they were easily distinguished by ^{1}H-NMR. *(αS,3S)-α-[(1S)-1,5-Dimethylhex-4-enyl]tatrahydro-5-oxafuran-3-aldehyde* (**20**): ^{1}H-NMR (300 MHz, $CDCl_3$): characteristic peaks at 9.80 (*d*, $J = 1.7$, 1 H); 1.16 (*d*, $J = 7.1$, 3 H) (**16**: 9.78 (*d*, $J = 1.8$, 1 H); 0.97 (*d*, $J = 7.0$, 3 H)).

(4S,5R,6R)-5-[(1S)-1,5-Dimethylhex-4-enyl]tetrahydro-4-(hydroxymethyl)-6-[(phenylseleno)methyl]-2H-pyran-2-one (**21**). A 0.05M soln. of $PhSeCH_2Li$ in THF was prepared by adding 1.6M BuLi in cyclohexane (0.83 ml, 1.37 mmol) to a soln. of bis(phenylseleno)methane (447 mg, 1.37 mmol) in dry THF (26 ml) at –78° under N_2 and stirring at this temp. for 45 min. A 9.8 ml (0.49 mmol) aliquot of this soln. was slowly introduced *via* syringe during 2.5 h to a soln. of **16** (100 mg, 0.42 mmol) in THF (100 ml) at –78°. The mixture was vigorously stirred at –78° for 1 h. Sat. NH_4Cl soln. was introduced and the org. phase washed with brine, dried, and evaporated. FC (silica gel, Et_2O/petroleum ether 4:6) of the residue provided **21** (85 mg) as a colorless oil and 45 mg of unreacted **16**. Yield of **21** based on recovered **16**, 90%. IR (neat): 3480, 1750, 1075. ^{1}H-NMR ($CDCl_3$): 7.54 (*m*, 2 H); 7.26 (*m*, 3 H); 4.98 (*m*, 1 H); 4.38 (*m*, 1 H); 3.55 (*m*, 1 H); 3.40 (*m*, 1 H); 3.24 (*m*, 1 H); 3.12 (*dd*, $J = 6.7, 13.1$, 1 H); 2.65 (*m*, 2 H); 2.42 (*m*, 1 H); 2.12 (*m*, 1 H); 2.02 (*m*, 1 H); 1.76 (*m*, 1 H); 1.67 (*s*, 3 H); 1.57 (*s*, 3 H); 1.64–1.46 (series of *m*, 1 H); 1.26 (*m*, 2 H); 1.13 (*m*, 1 H); 0.88 (*d*, $J = 6.8$, 3 H). ^{13}C-NMR ($CDCl_3$): 173.0, 133.3, 132.1, 129.9, 129.2, 127.4, 123.8, 78.5, 65.9, 43.7, 34.6, 33.5, 31.9, 31.8, 31.4, 25.7, 17.7, 17.0. MS: 410.1399 (M^+, calc. 410.1360).

(4S)-4,5-Dihydro-4-[(1R,2S)-1-[(1R)-1-hydroxy-2-(phenylseleno)ethyl]-2,6-dimethylhept-5-enyl]furan-2(3H)-one (**22**). A soln. of **21** (434 mg, 1.1 mmol) in benzene (434 ml) containing toluene-4-sulfonic acid (8 mg, 4 mol-%) was refluxed for 1 h, cooled to r.t., treated with 4 drops of pyridine, and evaporated. FC (silica gel, 10% petroleum ether/Et_2O) of the residue provided 245 mg of **22a** and 147 mg of unreacted **21**. **22a**: IR (neat): 3500, 1780. ^{1}H-NMR ($CDCl_3$): 7.51 (*m*, 2 H); 7.29 (*m*, 3 H); 4.97 (*m*, 1 H); 4.36 (*t*, $J = 8.2$, 1 H); 4.00 (*dd*, $J = 8.6, 10.1$, 1 H); 3.68 (*m*, 1 H); 3.12 (*dd*, $J = 3.3, 12.7$, 1 H); 2.99–2.70 (*m*, 2 H); 2.67–2.50 (*m*, 2 H); 2.34 (*dd*, $J = 11.4, 17.0$, 1 H); 1.90 (*m*, 2 H); 1.68 (*d*, $J = 0.9$, 3 H); 1.57 (*m*, 3 H); 1.50–1.30 (*m*, 1 H); 1.32–1.23 (*m*, 1 H); 1.08 (*m*, 1 H); 0.96–0.93 (*m*, 1 H); 0.89 (*d*, $J = 6.9$, 3 H). ^{13}C-NMR ($CDCl_3$): 177.4, 133.3, 132.0, 129.4, 128.9, 127.7, 123.8, 73.1, 67.9, 49.7, 37.8, 34.4, 34.0, 33.0, 25.9, 25.7, 16.2. MS: 410.1399 (M^+, calc. 410.1360).

(4S)-4,5-Dihydro-4-[(1R,2S)-1-[(1R)-1-(1-methoxy-1-methylethoxy)-2-(phenylseleno)ethyl]-2,6-dimethylhept-5-enyl]furan-2(3H)-one (**22b**). The sample of **22a** produced above was immediately taken up in 2-methoxypropene (5 ml) and stirred at 20° for 6 h in the presence of 1 drop of $POCl_3$. At this point, Et_3N (4 drops) was introduced and the mixture evaporated. FC (silica gel, petroleum ether/Et_2O 7:3 containing 5% of Et_3N) of the residue gave **22b** (250 mg, 74% overall). Colorless oil. $[\alpha]_D^{20} = -53.2$ ($c = 1.2$, $CHCl_3$). IR ($CHCl_3$): 1780. ^{1}H-NMR ($CDCl_3$): 7.54–7.49 (*m*, 2 H); 7.30–7.23 (*m*, 3 H); 5.05 (*m*, 1 H); 4.39 (*t*, $J = 8.3$, 1 H); 3.94 (*dd*, $J = 8.8, 10.4$, 1 H); 3.51 (*dd*, $J = 3.6, 12.6$, 1 H); 3.23 (*s*, 3 H); 2.99–2.85 (*m*, 2 H); 2.58 (*dd*, $J = 8.0, 17.0$, 1 H); 2.32 (*dd*, $J = 12.0, 17.0$, 1 H); 2.07–1.90 (series of *m*, 4 H); 1.70 (*d*, $J = 1.0$, 3 H); 1.61 (*s*, 3 H); 1.52–1.35 (series of *m*, 3 H); 1.29 (*s*, 3 H); 1.27 (*s*, 3 H); 0.85 (*d*, $J = 6.9$, 3 H). ^{13}C-NMR ($CDCl_3$): 177.4, 133.1, 131.9, 129.7, 129.2, 127.3, 124.1,

101.3, 72.9, 70.8, 48.9, 47.1, 35.7, 35.1, 34.7, 32.8, 32.2, 26.1, 25.9, 25.7, 24.5, 17.7, 16.2. MS: 449.1607 ($[M - MeOH_2]^+$, calc. 449.1595).

(3S,4R)-4,5-Dihydro-3-[(1'S and 1'R,2E)-1'-hydroxybut-2'-enyl]-4-{(1R,2S)-1-[(1R)-1-(1-methoxy-1-methylethoxy)-2-(phenylseleno)ethyl]-2,6-dimethylhept-5-enyl}furan-2(3H)-one (**23**). A cold (0°), magnetically stirred soln. of $(i\text{-}Pr)_2NH$ (0.28 ml, 2 mmol) in THF (85 ml) was treated slowly with 1.6M BuLi in cyclohexane (1.23 ml, 2 mmol), stirred for 45 min, and cooled to −78°. A soln. of **22b** (730 mg, 1.5 mmol) in dry THF was added dropwise and the mixture stirred for 2 h before crotonaldehyde (2.27 ml, 9 mmol) as a 4M soln. in THF (dried over sieves) was introduced. After quenching with sat. NH_4Cl soln., the phases were separated. The aq. layer was twice extracted with Et_2O and the combined org. soln. washed with sat. NH_4Cl soln., dried, and evaporated: 570 mg of yellow oil. This material was customarily subjected directly to acid-catalyzed cyclization. MPLC purification (silica gel, petroleum ether/Et_2O 6:4) gave the two pure epimers of **23**.

(1'S,2'E)-**23**: ^{1}H-NMR ($CDCl_3$): 7.57–7.51 (*m*, 2 H); 7.30–7.23 (*m*, 3 H); 5.87–5.76 (*m*, 1 H); 5.69 (*dd*, *J* = 16.4, 7.0, 1 H); 5.09 (*m*, 1 H); 4.63 (*t*, *J* = 9.4, 1 H); 4.25 (*m*, 1 H); 4.21 (*t*, *J* = 9.3, 1 H); 3.93 (*dd*, *J* = 2.7, 11.3, 1 H); 3.59 (*dd*, *J* = 2.9, 9.7, 1 H); 3.21 (*s*, 3 H); 2.92–2.75 (*m*, 2 H); 2.57 (*dd*, *J* = 5.9, 10.2, 1 H); 2.07 (*m*, 4 H); 1.77 (*d*, *J* = 6.3, 3 H); 1.71 (*s*, 3 H); 1.63 (*s*, 3 H); 1.52–1.35 (series of *m*, 3 H); 1.26 (*s*, 3 H); 1.24 (*s*, 3 H); 0.86 (*d*, *J* = 6.9, 3 H). ^{13}C-NMR ($CDCl_3$): 178.2, 133.4, 132.2, 130.3, 130.2, 129.9, 129.2, 127.4, 123.9, 101.3, 73.0, 72.3, 70.3, 48.6, 48.4, 43.9, 37.12, 37.09, 30.8, 30.0, 29.7, 25.9, 25.72, 25.65, 24.2, 18.0, 17.9. MS: 552.2365 (M^+, calc. 552.2354).

(1'R,2'E)-**23**: ^{1}H-NMR ($CDCl_3$): 7.69–7.51 (*m*, 2 H); 7.31–7.24 (*m*, 3 H); 5.85–5.73 (*m*, 1 H); 5.52 (*dd*, *J* = 7.4, 15.2, 1 H); 5.08 (*m*, 1 H); 4.42 (*t*, *J* = 9.1, 1 H); 4.20 (*t*, *J* = 9.3, 1 H); 3.93 (*dd*, *J* = 2.7, 11.2, 1 H); 3.61 (*dd*, *J* = 2.9, 12.5, 1 H); 3.21 (*s*, 3 H); 3.00–2.75 (*m*, 3 H); 2.70 (*dd*, *J* = 3.8, 10.7, 1 H); 2.10–1.95 (*m*, 3 H); 1.74 (*dd*, *J* = 0.9, 6.3, 3 H); 1.71 (*s*, 3 H); 1.64 (*s*, 3 H); 1.52–1.35 (series of *m*, 4 H); 1.26 (*s*, 3 H); 1.24 (*s*, 3 H); 0.89 (*d*, *J* = 6.7, 3 H). ^{13}C-NMR ($CDCl_3$): 178.5, 133.3, 132.2, 130.0, 129.9, 129.2, 129.1, 127.4, 123.8, 101.3, 72.0, 71.6, 70.6, 48.6, 48.5, 43.5, 37.1, 36.0, 30.8, 29.69, 29.65, 25.9, 25.6, 24.1, 17.9. MS: 552.2346 (M^+, calc. 552.2354).

Acid-Catalyzed Cyclization of **23**. The 570-mg sample of **23** produced above was dissolved in benzene (500 ml), treated with 30 mg (10 mol-%) of toluene-4-sulfonic acid, refluxed for 2 days, and cooled to r.t. A few drops of pyridine were added, and the solvent was evaporated. The residue was purified by MPLC (silica gel, petroleum ether/Et_2O 4:1): 240 mg (34%) of **24** and 260 mg (37%) of **25**.

When the *(1'R,2'E)*- and *(1'S,2'E)*-**23** were individually treated in analogous fashion, stereospecific conversion to **24** and **25**, respectively, occurred.

(3aS,4S,6S,7S,7aS)-7-[(1S)-1,5-Dimethylhex-4-enyl]-1,3a,4,6,7,7a-hexahydro-4-(prop-2-enyl)-6-(phenylthio)-3H-furo[3,4-c]pyran-3-one (**24**): Colorless oil. $[\alpha]_D^{20} = -70.7$ (*c* = 3.1, $CHCl_3$). IR ($CHCl_3$): 1740. ^{1}H-NMR ($CDCl_3$): 7.54–7.50 (*m*, 2 H); 7.36–7.32 (*m*, 3 H); 5.98–5.88 (*m*, 1 H); 5.50–5.43 (*m*, 1 H); 4.99 (*m*, 1 H); 4.84 (*m*, 1 H); 4.46 (*dd*, *J* = 6.5, 8.4, 1 H); 3.94 (*dd*, *J* = 8.4, 10.5, 1 H); 3.86 (*ddd*, *J* = 3.0, 9.0, 1 H); 3.24 (*dd*, *J* = 3.0, 9.0, 1 H); 3.07 (*dd*, *J* = 7.5, 9.0, 1 H); 2.60 (*dd*, *J* = 5.0, 13.5, 1 H); 2.43 (*dddd*, *J* = 13.5, 11.5, 6.5, 10.5, 1 H); 2.16–1.92 (*m*, 1 H); 1.90–1.77 (*m*, 1 H); 1.74 (*dt*, *J* = 6.6, 1.6, 3 H); 1.69–1.60 (series of *m*, 2 H); 1.65 (*d*, *J* = 0.8, 3 H); 1.58 (*s*, 3 H); 1.33 (*m*, 1 H); 1.10 (*m*, 1 H); 0.85 (*d*, *J* = 7.0, 3 H). *J*(3a,4) = 5, *J*(3a,7a) = 13.5, *J*(6,7) = 9.5, *J*(7,7a) = 11.5. ^{13}C-NMR ($CDCl_3$): 173.6, 132.9, 132.4, 131.5, 130.8, 129.0, 126.9, 124.2, 123.6, 71.8, 71.5, 70.8, 51.7, 47.1, 36.9, 32.3, 32.1, 31.7, 25.8, 25.8, 25.6, 19.2, 18.1, 17.7. MS: 462.1674 (M^+, calc. 462.1673).

(3aS,4R,6S,7S,7aS)-7-[(1S)-1,5-Dimethylhex-4-enyl]-1,3a,4,6,7,7a-hexahydro-4-(prop-2-enyl)-6-(phenylthio)-3H-furo[3,4-c]pyran-3-one (**25**): Colorless oil. $[\alpha]_D^{20} = -13.9$ (*c* = 2.0, $CHCl_3$). IR ($CHCl_3$): 1780. ^{1}H-NMR ($CDCl_3$): 7.57–7.50 (*m*, 2 H); 7.28–7.21 (*m*, 2 H); 5.85–5.71 (*m*, 2 H); 4.99 (*m*, 1 H); 4.45 (*dd*, *J* = 8.4, 6.1, 1 H); 3.94 (*m*, 2 H); 3.63 (*ddd*, *J* = 3.0, 7.0, 9.5, 1 H); 3.28 (*dd*, *J* = 3.0, 9.5, 1 H); 3.14 (*dd*, *J* = 7.0, 9.5, 1 H); 2.29 (*dddd*, *J* = 6.5, 10.5, 11.5, 13.0, 1 H); 2.08 (*dd*, *J* = 9.5, 13.0, 1 H); 2.08–1.98 (*m*, 1 H); 1.96–1.78 (*m*, 1 H); 1.74 (*dd*, *J* = 1.0, 5.9, 3 H); 1.73–1.60 (series of *m*, 2 H); 1.64 (*d*, *J* = 0.5, 3 H); 1.57 (*s*, 3 H); 1.35 (*m*, 1 H); 1.10 (*m*, 1 H); 0.87 (*d*, *J* = 7.1, 3 H). *J*(3a,4) = 9.5, *J*(3a,7a) = 13, *J*(6,7) = 9.5, *J*(7,7a) = 11.5. ^{13}C-NMR ($CDCl_3$): 173.2, 133.0, 132.5, 131.0, 129.0, 128.6, 127.2, 126.9, 123.6, 78.2, 77.4, 70.9, 50.5, 48.4, 43.0, 32.1, 31.7, 31.6, 25.8, 25.6, 19.1, 17.9, 17.7. MS: 462.1674 (M^+, calc. 462.1673).

(3aR,4R,7R,9aR)-4-[(1S)-Dimethylhex-4-enyl]-3a,6,7,9a-tetrahydro-7-methylcycloocta[c]furan-1,5-(3H,4H)-dione (**26**). To a soln. of **25** (40 mg, 0.50 mmol) in MeOH (15 ml) and H_2O (2 ml) was added sequentially Na_2CO_3 (47 mg, 0.56 mmol) and $NaIO_4$ (140 mg, 0.67 mmol). The heterogeneous mixture was stirred for 30 min, diluted with H_2O, and extracted with CH_2Cl_2. The separated org. phase was dried and evaporated. The residual selenoxide was dissolved in dry mesitylene (48 ml), treated with Et_2NH (0.21 ml, 2 mmol), and refluxed in an open vessel for 20 min. The cooled mixture was directly chromatographed (silica gel, petroleum ether (removal of mesitylene), then petroleum ether/Et_2O 7:3): **26** (120 mg, 80% overall). Colorless solid. M.p. 170° (from petroleum ether). $[\alpha]_D^{20} = +71.3$ (*c* = 0.83, $CHCl_3$). IR ($CHCl_3$): 1780, 1710. ^{1}H-NMR ($CDCl_3$): 5.71–5.57 (*m*, 2 H); 5.04 (*m*, 1 H); 4.42 (*dd*, *J* = 7.0, 9.0, 1 H); 3.90 (*dd*, *J* = 8.9, 11.2, 1 H); 3.24 (*dd*, *J* = 5.9, 12.7, 1 H); 3.08–3.00 (series of *m*,

2 H); 2.78 (*dd*, J = 5.2, 12.1, 1 H); 2.45–2.33 (*m*, 1 H); 2.21 (*t*, J = 12.6, 1 H); 2.07–1.94 (series of *m*, 3 H); 1.69 (*d*, J = 1.0, 3 H); 1.61 (*s*, 3 H); 1.35–1.20 (series of *m*, 2 H); 1.17 (*d*, J = 6.5, 3 H); 1.07 (*d*, J = 6.9, 3 H). NOE: irrad. at H_β–C(3) → 3% at H–C(9a); irrad. at H–C(9a) → 8% at H_β–C(4), 8% at H_β–C(7). ^{13}C-NMR ($CDCl_3$): 210.7, 176.4, 139.9, 132.2, 123.8, 123.5, 69.8, 58.0, 54.9, 45.5, 42.8, 35.1, 34.4, 29.5, 25.9, 25.7, 20.6, 17.7, 14.6. MS: 304.2035 (M^+, calc. 304.2038). Anal. calc. for $C_{19}H_{28}O_3$: C 74.96, H 9.27; found: C 74.70, H 9.35.

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