Synthesis of Limonoid Model Insect Antifeedants through Stereoselective Aldol Addition Reactions

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The aldol condensation of 3-furaldehyde and enol silanes or enolates (Li, Mg, and Ti) of 2,6-dimethyl- and 2,2,6-trimethylcyclohexanones has been investigated (Tables I, II and Chart II). The reaction of dimethyl enol silane 1 showed poor facial and diastereoselectivity. Enol silane 1′ showed a synthetically useful *u1* selectivity (100%). The lithium enolate of 2,6-dimethylcyclohexanone showed good facial and diastereoselectivity as did the magnesium enolate of 2,2,6-trimethylcyclohexanone. These results were applied to the preparation of limonoid model compounds **5a–d** (Scheme I) and **5′a,b** (Scheme II) by a short and selective route. The synthesis of (±)-pyroangolensolide (Scheme III) was achieved in a 33% overall yield from 2,6-dimethylcyclohexanone.

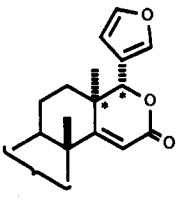
Introduction

Fragment A (Chart I) represents a "structural unit" very common in the limonoid family and related triterpene metabolites.[1] Despite their biological properties and unique structure, very few synthetic approaches to limonoids in general,[2] and to fragment A, in particular,[3] have been reported. We started a research program directed toward the synthesis of both limonoids and fragment A.[4]

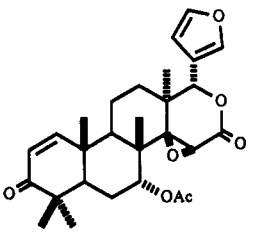
One of the shortest ways to accomplish the creation of the two chiral centers in A in a single step is an aldol condensation. Over the last 15 years considerable research has been dedicated to controlling the stereochemical course of this reaction, which is one of the most important methods for the formation of carbon–carbon bonds in organic synthesis.[5] In connection with a search for simple synthetic methods[4] applicable to limonoids, such as gedunin,[6] or related structural fragments, such as pyroangolensolide[7] (Chart I), we undertook a stereochemical study of the reaction between 3-furaldehyde and the enol silanes or enolates (Li, Mg and Ti) of 2,6-dimethyl- and 2,2,6-trimethylcyclohexanones (Scheme I).

The influence of methyl subsituents on the stereochemical course of cyclohexanone aldol reactions has not been studied in depth,[5b,8] and hence our approach, although primarily directed to limonoids, should be of general interest.

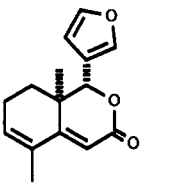
Chart I



A

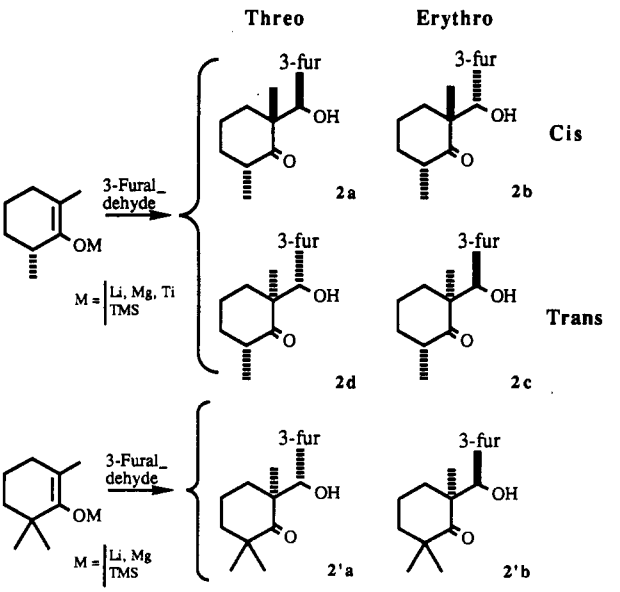


Gedunin



Pyroangolensolide

Scheme I. Isomers from Aldol Addition[a]



[a] All synthesized compounds are racemic modifications although only one enantiomer is depicted.

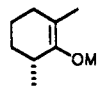
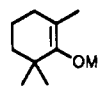
Results and Discussion

Diastereoselection. Enol Silanes. Enol silanes 1 and 1′ (Table I) were obtained from the corresponding ketones by a previously reported procedure,[9] and their Lewis acid

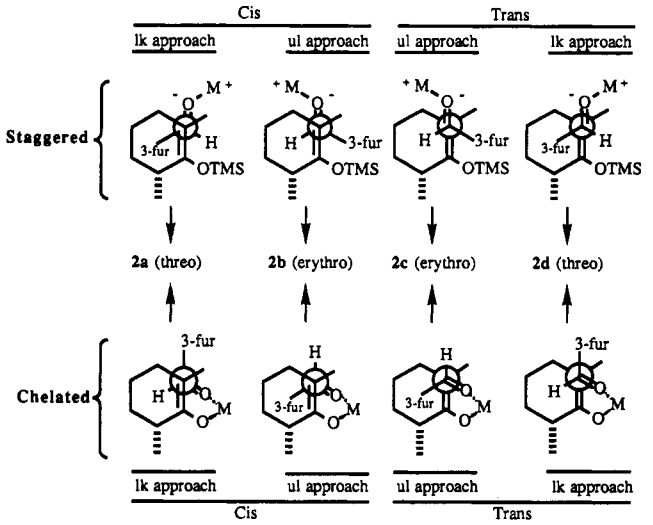
(1) Taylor, D. A. H. *Prog. Chem. Org. Nat. Prod.* **1984**, *45*, 1.
(2) (a) Corey, E. J.; Reid, J. G.; Myers, A. G.; Hahl, R. W. *J. Am. Chem. Soc.* **1987**, *109*, 918. (b) Corey, E. J.; Hahl, R. W. *Tetrahedron Lett.* **1989**, *30*, 3023.
(3) (a) Tokoroyama, T.; Fukuyama, Y.; Ketsuji, Y. *J. Chem. Soc., Perkin Trans. 1* **1988**, 445. (b) Drews, S. E.; Grieco, P. A.; Huffman, J. C. *J. Org. Chem.* **1985**, *50*, 1309. (c) Lottenbach, W.; Graf, W. *Helv. Chim. Acta* **1978**, *61*, 3087.
(4) Mateos, A. F.; Blanco, J. A. de la F. *J. Org. Chem.* **1990**, *55*, 1349.
(5) (a) Evans, D. A.; Nelson, J. O.; Taber, T. R. *Top. Stereochem.* **1983**, *13*, 1–113. (b) Heathcock, C. H. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, pp 111–212. (c) Masamune, S.; Choy, W.; Petersen, J. S.; Sita, R. L. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1.
(6) (a) Akisanya, A.; Bevan, C. W. L.; Hirst, J.; Halsall, T. G.; Taylor, D. A. H. *J. Chem. Soc. C* **1960**, 3827. (b) Khalid, S. A.; Duddeck, H.; Sierra, M. G. *J. Nat. Prod.* **1989**, *52*, 922.
(7) (a) Davis, J. B.; Godfrey, V. M.; Jewers, K.; Manchanda, A. H.; Robinson, F. V.; Taylor, D. A. H. *Chem. Ind. (London)* **1970**, 201. (b) Jewers, K.; Manchanda, A. H.; Taylor, D. A. H. *Ibid.* **1972**, 976.
(8) (a) Nakamura, E.; Kuwajima, I. *Tetrahedron Lett.* **1983**, *24*, 3343. (b) Nakamura, E.; Shimizu, M.; Kuwajima, I.; Sakata, J.; Yokoyama, K.; Noyori, R. *J. Org. Chem.* **1983**, *48*, 932. (c) Heathcock, C. H.; Buse, C. T.; Kleschick, W. A.; Pirrung, M. C.; Sohn, J. E.; Lampe, J. *Ibid.* **1980**, *45*, 1066. (d) Although the reaction between benzaldehyde and cyclohexanone lithium enolate or enol silane had been presumably well studied, new data concerning the erythro/threo diastereomer ratio have been provided by: Majewski, M.; Gleave, D. M. *Tetrahedron Lett.* **1989**, *30*, 5681.

0022-3263/91/1956-7084$02.50/0

Table I. Diastereoselection

compd	M	time	Aldols, % in mixture 2a	2b	2c	2d	% in mixture cis	trans	% in mixture erythro	threo	isolated yield (%)
 1	TMS	1m/1h	11	26	39	24	37	63	66	34	71
		5s	7	–	15	78	7	93	15	85	47
		10s	25	–	23	52	25	75	23	77	73
	Li	1min	23	–	31	46	23	77	31	69	92
		60min	32	8	30	30	41	60	39	62	93
	Ti	25min	22	–	35	43	22	78	35	65	65
	Mg	5min	43	–	36	21	43	57	36	64	50
 1'	TMS	30min							100	0	67
	Li	5s							26	74	40
	Mg	4min							0	100	52

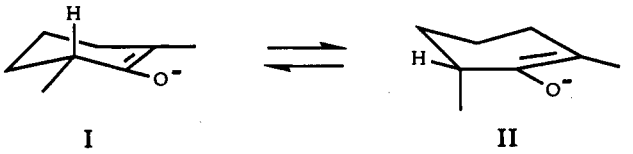
Scheme II. Transition States



catalyzed aldol condensations were studied. Titanium(IV) chloride was employed as the Lewis acid, and the reactions were carried out in methylene chloride at −78 °C. Control experiments showed no product ratio time dependence over periods ranging from 1 to 60 min. The data show that there is a low degree of stereoselection for dimethyl enol silane **1**, and a mixture of the four possible diastereoisomers (Scheme I) is obtained. The facial selectivity (trans–cis) and the erythro–threo ratio are approximately 2:1. The trimethyl enol silane **1'**, however, gives a single product in 67% isolated yield, identified as the erythro isomer **2'b**. This latter result is not compatible with a Zimmerman–Traxler[10] chelated transition state but rather with a staggered transition state as proposed by Heathcock et al.[11] (Scheme II) and demonstrated by Denmark and Henke;[12] this would also explain the relative preference for the erythro diastereoisomers found with the dimethyl enol silane **1**.

Diastereoselection. Enolates. Lithium enolates were prepared by treatment of the corresponding ketones with lithium diisopropylamide in ether at −78 °C. Titanium enolates were obtained from the lithium enolates by reaction with $Ti(i\text{-}PrO)_3Cl$ in ether at −30 °C. Magnesium enolates were prepared from the enol silanes by bromination with *N*-bromosuccinimide at 0 °C, followed by treatment of the bromo ketone with magnesium turnings

Scheme III. Enolate Conformations



I II

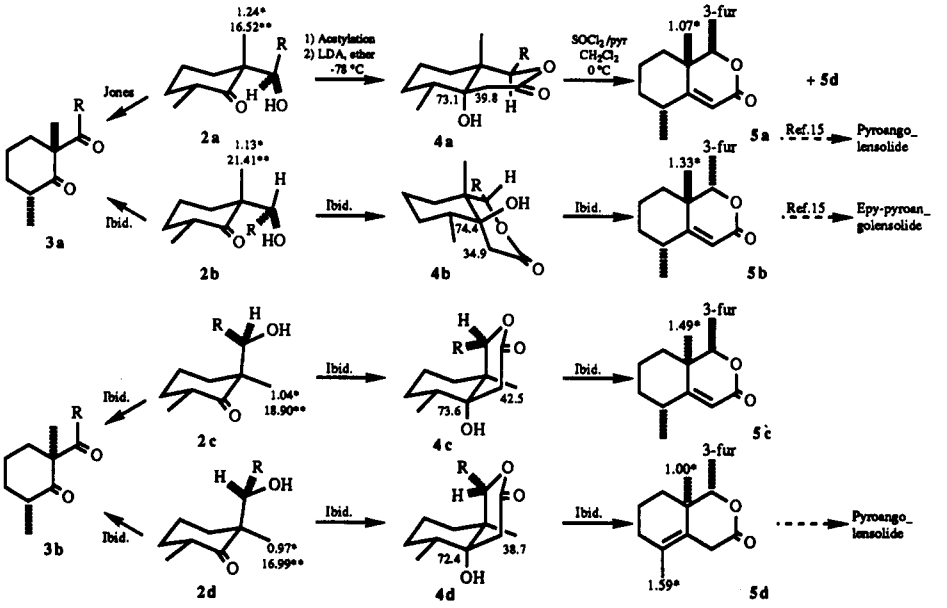
in a benzene/ether mixture. All aldol reactions were carried out in ether, at −78 °C for the lithium and titanium enolates and at 0 °C for the magnesium enolates. The results are summarized in Table I.

For the lithium enolate from 2,6-dimethylcyclohexanone, a significant selectivity is observed at very short reaction times. This selectivity decreases for longer reaction periods due to reversibility. A perference for the *lk* approach, which affords the threo isomers, is observed as expected from the chelated transition states depicted in Scheme II. A facial bias (trans) is also observed comparable to that reported by House et al.[13] for an analogous reaction. There is an apparent preference for axial (trans) approach of the electrophile to enolate through conformation I (Scheme III). The facial selectivity and the absence of cis-erythro isomer **2b** in the product mixture could also be explained assuming that enolate conformation II makes a significant albeit presumably minor contribution to the reaction. In this case, axial attack (cis) would be hindered by the 6-methyl group and equatorial (trans) attack would be preferred. No relevant differences were found for titanium enolates with respect to the lithium ones. A tighter chelated transition state is expected from the more covalent magnesium enolate which decreases axial (trans) attack[14] to the supposedly major enolate I. Thus, more of **2a** is formed by the approach of the aldehyde from the more sterically accessible equatorial direction. We have no explanation to justify the observed predominance of erythro over threo among the trans diastereoisomers in the case of magnesium enolate, although aggregation effects should not be ignored.

The lithium enolate from 2,2,6-trimethylcyclohexanone shows a similar relative topicity to that observed for the enolate from 2,6-dimethylcyclohexanone. This diastereoselectivity is enhanced by use of the magnesium enolate of the trimethylcyclohexanone to give up to 100% of the threo isomer **2'a** (Scheme I), which, from the point of view of synthesis, makes this reaction useful. Given the fact that the enol silanes prefer a nonchelated transition state and the metal enolates react via a Zimmerman–Traxler transition state (Scheme II), the results obtained from the

(9) Cazeau, P.; Duboudin, F.; Moulines, F.; Babot, O.; Dunogues, J. *Tetrahedron* **1987**, *43*, 2075.
(10) Zimmerman, H. E.; Traxler, M. D. *J. Am. Chem. Soc.* **1957**, *79*, 1920.
(11) Heathcock, C. H.; Davidsen, S. K.; Huy, K. T.; Flippin, L. A. *J. Org. Chem.* **1986**, *51*, 3027.
(12) Denmark, S. E.; Henke, B. R. *J. Am. Chem. Soc.* **1989**, *111*, 8032.
(13) House, H. O.; Crumrine, D. S.; Teranishi, A. Y.; Olmstead, H. D. *J. Am. Chem. Soc.* **1973**, *95*, 3310.
(14) Trost, B. M.; Florez, J.; Jebaratnam, D. J. *J. Am. Chem. Soc.* **1987**, *109*, 613.

Scheme IV. Chemical and Spectroscopical Evidences[a]



[a] R = 3-fur. *Chemical shifts of protons (ppm). **Chemical shifts of the carbon (ppm).

addition of 3-furaldehyde to the enol silane 1′ (M = TMS, *ul* approach, 100% erythro) and to the magnesium enolate 1′ (M = Mg, *lk* approach, 100% threo) suggest that the *gem*-dimethyl group is responsible for the excellent stereoselectivity observed.

The stereostructures assigned to aldols **2a–d** are supported by the following: (i) chemical correlation with the known pyroangolensolide and *epi*-pyroangolensolide whose structures have been assigned by Grieco et al.[3b] on the basis of single-crystal X-ray analysis and (ii) physical and spectroscopic comparison of **5a** and **5b** (Scheme IV) with the same compounds recently obtained by Bentley et al.[15] via a longer procedure.

We have also obtained independent verifications of these assignments from spectroscopic data and chemical evidence. Jones oxidation carried out independently with the aldols **2a** and **2b** (Scheme IV) provided the same diketone **3a**, which means they are erythro and threo isomers and only differ in the relative configuration of the carbon atom supporting the hydroxy group. An analogous experiment with **2c** and **2d** yielded diketone **3b**. The axial orientation of the 3-furylhydroxymethyl group in isomers **2c** and **2d** is indicated by the fact[13] that these two isomers underwent a more rapid retroaldol decomposition upon treatment with base than the two equatorial isomers **2a** and **2b**.[16]

The assignments of erythro and threo configurations to the pair of axial isomers **2c** and **2d** and to the pair of equatorial isomers **2a** and **2b** was made tentatively by comparison with House[13] and Kuwajima's[17] aldols. It will be seen later that these tentative assignments were correct. In the axial pair **2c,d**, the signal of the methyl group geminal to 3-furylhydroxymethyl appears at a higher field for threo isomer **2d** in both ^1H and ^{13}C NMR spectra. In the equatorial pair **2a,b**, the resonance of the methyl group occurs upfield in the ^1H NMR spectrum of erythro isomer **2b** while in the ^{13}C NMR spectrum it is downfield relative to threo **2a**. Our ^1H NMR values agree with those reported by House and Kuwajima, and hence this could be a method for assigning the structures of this type of compound.

The intramolecular aldol reaction of each keto acetate from **2a–d** promoted by lithium diisopropylamide in ether at −78 °C gave only one hydroxy lactone **4a–d** in 90–97% yield (Scheme IV). The structures proposed for these hydroxy lactones were supported by ^1H and ^{13}C NMR spectra and by the structure of the products resulting from dehydration with thionyl chloride. The stereochemical outcome of the cyclization of each keto acetate to the corresponding cis or trans bicyclic hydroxy lactone can be rationalized by considering steric factors, as postulated by Spencer.[18] The cyclization process in this type of compound is governed by the size of incipient angular substituent (in this case a large methyl group). In agreement with this postulate, the cis bicyclic isomer is expected for keto acetates from **2c** and **2d** with an axial 3-furylacetoxymethyl group. Cyclization leading to a trans hydroxy lactone would be rather difficult because the two axial methyl groups flanking the carbonyl group prevent equatorial attack. The intermediate for keto acetates **2a** and **2b**, which would afford the trans ring junction, has an incipient axial methyl group and also an equatorial one; the former prevents equatorial attack while the latter reinforces this attack.[19] While Spencer's postulate undoubtedly predicts a cis ring junction for the cyclization of **2c,d**, the mode of cyclization for **2a,b** is a priori very doubtful. To resolve this problem we analyzed the ^{13}C NMR shifts; this has proved useful in assigning stereochemistry to similar cases[14,19b]. The signal for the α-methylene group to the carbonyl group appears at higher field for the axial isomer than for the equatorial isomer; in addition, the carbinol carbon appears at lower field for an equatorial hydroxyl group. Scheme IV shows the most

(15) Bentley, M. D.; Rajab, M. S.; Mendel, M. J.; Alford, A. R. *J. Agric. Food Chem.* **1990**, *38*, 1400.

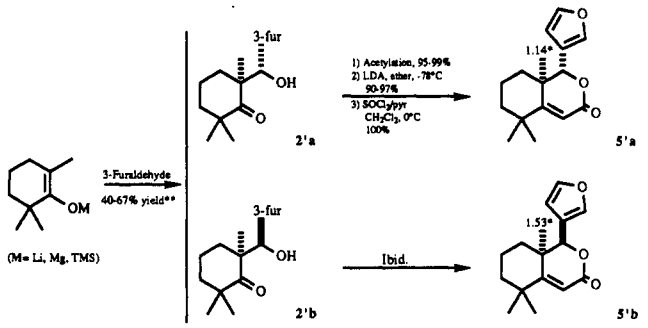
(16) A solution of each of the aldols **2a–d**, 1 mmol in CCl_4 (0.2 mL), was treated independently with 50 μL of an aqueous solution of KOH (12 M) at room temperature. Aldols **2a** and **2b** took 24 h to undergo total retroaldol decomposition, while both **2c** and **2d** took only 3 h.

(17) The threo isomer depicted below has been analyzed by X-ray.[8b]

(18) (a) Spencer, T. A.; Neel, H. S.; Ward, D. C.; Williamson, K. L. *J. Org. Chem.* **1966**, *31*, 434. (b) Deslongchamps, P. In *Stereoelectronic Effects in Organic Chemistry*; Pergamon Press: Oxford, 1983; p 304.

(19) (a) Makherjee, D.; Wu, Y.-D.; Fronczek, F. R.; Houk, K. N. *J. Am. Chem. Soc.* **1988**, *110*, 3328. (b) Nussbaumer, C. *Helv. Chim. Acta* **1990**, *73*, 1621 and references cited therein.

Scheme V. Compounds from 2,2,6-Trimethylcyclohexanone[a]



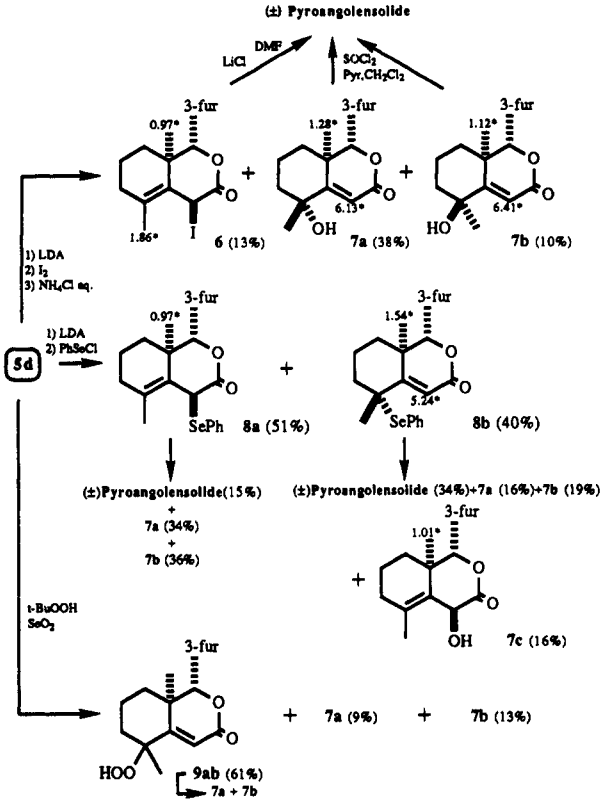
[a] *Chemical shifts of protons (ppm). **Isolated yields; in all cases quite a lot of 2,2,6-trimethylcyclohexanone was recovered.

probable structures for hydroxy lactones **4a–d**. The difference in the mode of cyclization for **2b** with respect to **2a** can be attributed to the 1,3-diaxial nonbonded interaction developed between the oxygen atom and the furyl group in the transition state to give the trans ring junction.

The dehydration of hydroxy lactones **4a–d**, with $SOCl_2$/pyr in CH_2Cl_2 at 0 °C for 5 min,[20] gave the unsaturated lactones **5a–d** in quantitative yields. Compounds **5a** and **5b** are identical with those reported by Bentley et al.[15] A common feature of unsaturated lactones **5a–d** is the high-field position of the angular methyl group signal in the ^1H NMR spectrum when they are cis with respect to the furan ring relative to the trans isomers. This has been applied to assignments of relative configuration in aldols **2'a** and **2'b** correlated to the trimethyl α,β-unsaturated lactones **5'a** and **5'b** prepared by a parallel sequence (Scheme V).

Transformation of unsaturated lactone **5d** into pyroangolensolide was carried out by three different procedures (Scheme VI). The first consisted of an iodination–dehydroiodination process. The initial reaction was carried out by treatment of the lithium dienolate from **5d** with iodine and essentially gave the same results under both kinetic and thermodynamic conditions.[21] The three products (in order of elution from SiO_2) isolated were identified as the 4-iodo lactone **6** and the 5-hydroxylated products **7a** and **7b**.[22] These structures are supported by ^1H NMR data. The assignment of a trans relationship between the iodine atom and the angular methyl group in **6** is based on the counter-balancing influence on the resonance of this methyl group by of iodine and the paramagnetic shift caused on the methyl group attached to C-5 relative to that of the same methyl group in **5d** (Scheme VI). These data are in agreement with steric demands in the approach of iodine to the dienolate. The vinylic H-4 appears at a low field for **7b** relative to **7a**. This downfield shift is caused by the hydroxy group which is in the same plane as H-4. The same argument must account for the downfield shift for the angular methyl group in **7a** relative to **7b**. The two hydroxylated products **7a** and **7b** must have been formed in the workup by solvolysis of the formerly produced 5-iodo lactone. Dehydrohalogenation of the 4-iodo lactone **6** to pyroangolensolide was effected in 87% yield with LiCl in DMF under reflux; this compound is identical with that

Scheme VI. (±) Pyroangolensolide from 5d[a]



[a] *Chemical shifts of protons (ppm).

reported by Grieco et al.[3b] Both hydroxylated products, **7a** and **7b**, were dehydrated independently with $SOCl_2$ in pyridine at 0 °C to give pyroangolensolide in quantitative yield.

The second method selected to transform **5d** into pyroangolensolide was selenenylation followed by oxidation–elimination. The addition of PhSeCl to the lithium dienolate[23] in THF at −78 °C over 3 h gave two compounds in a 5:4 ratio which were separated by chromatography. The major and less polar compound was identifed as **8a**, whose structure is supported by the same arguments given for 4-iodo lactone **6**; structure **8b** was assigned to the minor selenide. The low-field displacement of the angular methyl group in **8b** is justified by the paramagnetic shift induced by the selenium atom located at a cis orientation relative to the above-mentioned methyl group. Treatment of **8a** with H_2O_2 in THF/AcOH at 0 °C for 30 min[24] afforded a mixture of pyroangolensolide and the hydroxy lactones **7a** and **7b**. The lack of stereoselectivity in the [2,3]-sigmatropic rearrangement of allyl selenoxide from **8a** could be due to acetic acid.[25] After oxidation, allyl selenide **8b** gave the same products obtained from **8a**, together with the 4-hydroxylated product **7c**.

Treatment of **5d** with a catalytic amount of SeO_2[26] and 1 equiv of *tert*-butylhydroperoxide in CH_2Cl_2 at room temperature and open to the air gave a mixture of hy-

(20) Saunders, W. H., Jr. In *The Chemistry of Alkenes*; Patai, S., Ed.; J. Wiley: London, 1964; pp 168–176.

(21) (a) Rathke, M. W.; Lindert, A. *Tetrahedron Lett.* **1971**, 3995. (b) Arnold, R. T.; Kulenovic, S. T. *J. Org. Chem.* **1978**, *43*, 3687.

(22) Between the halogenated compound **6** and the hydroxylated product **7a**, mixtures of Michael addition products together with starting material were eluted but not identified; to avoid these additions, we prepared the dienolate with a mixture of LDA and HMPA (1:1) as reported by: Schlessinger, R. H. et al. *Tetrahedron Lett.* **1973**, 2433. Unfortunately, the results were very similar.

(23) (a) Fleming, I.; Goldhill, J.; Paterson, I. *Tetrahedron Lett.* **1979**, 3205. (b) The addition of PhSeCl to the dienol silane from **5d** in CH_2Cl_2 at −78 °C afforded a complex mixture of compounds. From the ^1H NMR spectra of the crude products we estimated the presence of the selenide products **8a** (24%) and **8b** (10%).

(24) Sharpless, K. B.; Lauer, R. J. *J. Am. Chem. Soc.* **1972**, *94*, 7154.

(25) In some cases the carbonium ion has been reported as an intermediate: Reich, M. J. In *Oxidation in Organic Chemistry*; Trahanovsky, W. S., Ed.; Academic Press: New York, 1978; Part C, pp 102–107.

(26) This oxidant was chosen for its innocuous character with respect to furan, as we have shown: Mateos, A. F.; Barrueco, O. F.; González, R. R. *Tetrahedron Lett.* **1990**, *31*, 4343.

droperoxides **9a:b** (1.0:1.4 ratio from its ^1H NMR spectra) and the hydroxylated products **7a** and **7b**. The latter compounds are those expected from an ordinary SeO_2 oxidation, but the former could be explained in terms of a radical reaction induced by SeO_2.[27] Reduction of the hydroperoxide mixture **9a/b** with $NaBH_4$ in MeOH at 0 °C gave the hydroxylated products **7a** and **7b** almost quantitatively.

The efficient synthesis of pyroangolensolide reported in this paper was achieved in 33% overall yield[28] from 2,6-dimethylcyclohexanone and is competitive with all previous syntheses.[3a,b] The strategy shown here should also be applicable to the synthesis of more complex analogues and archetype limonoids. The study of structure–antifeedant activity relationships is currently under way and will be reported elsewhere.

Experimental Section

General Methods. Melting points were determined on a hot-stage apparatus and are not corrected. The ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution at 200 MHz for proton. IR spectra were obtained as thin films. Reactions requiring anhydrous conditions were performed in flame-dried glassware under a positive pressure of dry N_2. All reactions were monitored by TLC. Flash column chromatographies were carried out using silica gel 60 (0.040–0.063-mm Merck). Organic extracts were dried with anhydrous Na_2SO_4 and evaporated under reduced pressure below 40 °C. All crystalline product were recrystallized from hexane/ether.

2-(3-Furylhydroxymethyl)-2,6-dimethylcyclohexanones 2a–d. A. Via the Enol Silane. $TiCl_4$ (0.22 mL, 1.98 mmol) was added at −78 °C with stirring under N_2 to a solution of 3-furaldehyde (153 mg, 1.59 mmol) in dry CH_2Cl_2 (9 mL). Immediately a yellowish solid was formed and to the resulting heterogeneous mixture a solution of the enol silane **1**[29] (315 mg, 1.59 mmol) in dry CH_2Cl_2 (10 mL) was added.

The solid disappeared immediately, and the resulting red mixture was stirred at −78 °C for 1 min.[30] Aqueous Na_2CO_3 (7 mL, 10%) was added, and the resulting heterogeneous mixture was stirred and gradually warmed to rt (1 h). The organic layer was separated, and the aqueous phase was extracted twice with CH_2Cl_2. The combined extracts were washed with water and brine and then dried (Na_2SO_4). Evaporation of the solvent left a crude product (350 mg) of four different aldol compounds which were separated by flash chromatography using hexane–ether (7:4) as the eluent.

The first one eluted (28 mg, 8% yield) was a crystalline product identified as **(2*RS*,6*RS*)-2-[(*SR*)-3-furylhydroxymethyl]-2,6-dimethylcyclohexanone (2a)**: mp 134–135 °C; IR 3503, 1688, and 1600 cm^{-1}; ^1H NMR δ 1.02 (3 H, d, J = 6.4 Hz, CH_3-6), 1.24 (3 H, s, CH_3-6), 2.65 (1 H, m, H-6), 4.05 (1 H, d, J = 2.0 Hz, OH), 4.85 (1 H, d, J = 2.0 Hz, CH-Fur), 6.35 (1 H, m, H-β'), 7.34 (1 H, m, H-α), and 7.35 (1 H, m, H-α'); ^{13}C NMR δ 14.44, 16.52, 20.74, 36.40, 37.20, 41.41, 52.22, 71.96, 110.26, 123.94, 140.41, 142.13, and 208.22; MS m/z (relative intensity) 222 (8, M^+), 126 (100), 111 (76), 97 (56), 84 (37), 69 (22), and 55 (22). Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 70.29; H, 8.22.

The second compound (67 mg, 19% yield) was a crystalline product identified as **(2*RS*,6*RS*)-2-[(*RS*)-3-furylhydroxymethyl]-2,6-dimethylcyclohexanone (2b)**: mp 72–73 °C; IR 3506, 1690, and 1600 cm^{-1}; ^1H NMR δ 1.02 (3 H, d, J = 6.4 Hz, CH_3-6), 1.13 (3 H, s, CH_3-2), 2.64 (1 H, m, H-6), 3.30 (1 H, d, J = 2.0 Hz, OH), 4.90 (1 H, d, J = 2.0 Hz, CH-Fur), 6.34 (1 H, m, H-β'), 7.32 (1 H, m, H-α), and 7.34 (1 H, m, H-α'); ^{13}C NMR δ 14.52, 20.67, 21.41, 32.37, 35.76, 41.69, 52.85, 71.19, 110.21, 124.11, 140.23, 142.17, and 218.94. Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 70.30; H, 8.21.

The third compound (95 mg, 27% yield) was an oily product identified as **(2*RS*,6*SR*)-2-[(*RS*)-3-furylhydroxymethyl]-2,6-dimethylcyclohexanone (2c)**: IR 3610–3200, 3148, and 1703 cm^{-1}; ^1H NMR δ 1.02 (3 H, d, J = 6.4 Hz, CH_3-6), 1.04 (3 H, s, CH_3-2), 2.60 (1 H, m, H-6), 5.03 (1 H, s, CH-Fur), 6.22 (1 H, m, H-β'), 7.28 (1 H, m, H-α), and 7.32 (1 H, m, H-α'); ^{13}C NMR δ 15.23, 18.90, 19.16, 33.62, 33.77, 43.09, 53.34, 70.26, 109.34, 125.46, 139.85, 142.87, and 217.48.

The fourth compound (60 mg, 17% yield) was a crystalline product identified as **(2*RS*,6*SR*)-2-[(*SR*)-3-furylhydroxymethyl]-2,6-dimethylcyclohexanone (2d)**: mp 117–118 °C; IR 3460–3300, 1694, and 1597 cm^{-1}; ^1H NMR δ 0.97 (3 H, s, CH_3-2), 1.05 (3 H, d, J = 6.5 Hz, CH_3-6), 2.78 (1 H, m, H-6), 5.24 (1 H, s, CH-Fur), 6.37 (1 H, m, H-β'), 7.38 (1 H, m, H-α), and 7.39 (1 H, m, H-α'); ^{13}C NMR δ 15.12, 16.99, 20.36, 35.80, 36.98, 41.42, 53.12, 70.03, 109.72, 124.82, 140.12, 142.73, and 218.00; MS m/z (relative intensity) 222 (2, M^+), 175 (2), 149 (2), 137 (3), 126 (100), 111 (71), 97 (60), 84 (32), 69 (25), and 55 (24). Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 70.29; H, 8.24.

B. Via the Magnesium Enolate. One drop of a solution of the 2-bromo-2,6-dimethylcyclohexanones[31] (814 mg, 3.97 mmol) in dry benzene (2.2 mL) and dry ether (1.1 mL) was added, under N_2 at rt and without stirring, to a heterogeneous mixture of Mg turnings (94 mg, 3.97 mat-g) in dry ether (1.1 mL) and two drops of 1,2-dibromoethane. When the bubbling stopped, the rest of the solution of the α-bromo ketones was slowly added dropwise. After 2 min it was necessary to stir the mixture to keep the bubbling, thereafter warming the mixture at 50 °C for an additional 30 min to dissolve all the Mg.

The mixture was then cooled at 0 °C, and 3-furaldehyde (0.35 mL, 3.97 mmol) was added rapidly with stirring. After 5 min aqueous buffer solution at pH 7 (KH_2PO_4–NaOH, 3 mL) was added and the resulting heterogeneous mixture was stirred and gradually warmed to rt. The organic layer was separated, and the aqueous phase was extracted twice with ether. The combined extracts were washed with water and brine and then dried (Na_2SO_4). Evaporation of the solvent left a crude product mixture (774 mg) which was chromatographed using hexane–ether (7:4) as the eluent.

The reaction products were isomers **2a** (190 mg, 22% yield), **2c** (158 mg, 18% yield), and **2d** (92 mg, 10% yield).

C. Via the Lithium Enolate. A solution of BuLi (3.6 mL, 5.5 mmol) in hexane (1.5 M) was added dropwise at 0 °C with stirring under N_2 to a solution of diisopropylamine (0.8 mL, 5.5 mmol) in ether (10.0 mL) with 2,2′-bipyridine (2 mg, 0.01 mmol) as indicator. The resulting dark red mixture was stirred at 0 °C for an additional 15 min. The mixture was then cooled at −78 °C, and the 2,6-dimethylcyclohexanone (630 mg, 5.0 mmol) was added dropwise over 5 min until the mixture became yellow. Stirring was continued at −78 °C for 15 min; then 3-furaldehyde (0.44 mL, 5.0 mmol) was added rapidly. After the chosen time (5 s, 10 s, 1 min or 1 h) an saturated aqueous NH_4Cl (10.0 mL) was added and the resulting heterogeneous mixture was stirred and gradually warmed to rt (1 h). The organic layer was separated, and the aqueous phase was extracted twice with ether. The combined extracts were washed with water and brine and then dried (Na_2SO_4). Evaporation of the solvent left crude product mixtures which were separated by flash chromatography. Yields and ratios at different reaction times are shown in Table I.

D. Via the Titanium Enolate. A solution of $Ti(i\text{-}PrO)_3Cl$ (12.6 mmol)[32] in dry ether (1 mL) was added dropwise at −30 °C with stirring under N_2 to a solution of the lithium enolate (3.97 mmol) of the 2,6-dimethylcyclohexanone (500 mg, 3.97 mmol) in dry ether (8 mL). This was prepared as shown in the preceding

(27) Umbreit, M. A.; Sharpless, K. B. *J. Am. Chem. Soc.* **1977**, *99*, 5526.

(28) The sequence [1 → **2a/d** → **5d** → **8a/b** → (**7a/b** + piroangolensolide)] was used to calculate this 33% yield.

(29) 2,6-Dimethyl-1-(trimethylsiloxy)cyclohexene (1) and 2,6,6-trimethyl-1-(trimethylsiloxy)cyclohexene (1′) were prepared as reported by P. Cazeau et al.[9] from the corresponding cyclohexanone; 1 h was required to complete the reaction.

(30) Longer time periods (5 min, 30 min, or 1 h) gave similar yields and similar ratios in the corresponding aldol compounds.

(31) A mixture of the 2-bromo-2,6-dimethylcyclohexanones was prepared as reported by: Reuss, R. H.; Hassner, A. *J. Org. Chem.* **1974**, *39*, 1785 from the corresponding enol silane. To complete the reaction 15 min were required and a 98% yield was obtained.

(32) This solution was prepared by mixing under N_2 at room temperature $Ti(i\text{-}PrO)_4$ (2.81 mL, 9.45 mmol) and $TiCl_4$ (0.34 mL, 3.15 mmol) in dry ether (1 mL).

reaction. Immediately a yellowish solid was formed; the heterogeneous mixture was stirred at −30 °C for an additional 30 min and then cooled at −78 °C and stirred for 2 h at this temperature. 3-Furaldehyde (0.34 mL, 3.97 mmol) was added rapidly. After 25 min a saturated aqueous NH_4Cl (10 mL) was added and the resulting heterogeneous mixture was stirred and gradually warmed to rt. After the usual workup the crude product mixture was flash chromatographed.

The products were isomers **2a** (123 mg, 14% yield), **2c** (203 mg, 23% yield), and **2d** (248 mg, 28% yield).

2-(3-Furylhydroxymethyl)-2,6,6-trimethylcyclohexanones (2′a,b). A. Via the Enol Silane. The enol silane 1′ (337 mg, 1.59 mmol) from 2,2,6-trimethylcyclohexanone[29] was treated as in a previous procedure to obtain only an aldol product identified as **(2*RS*)-2-[(*RS*)-3-furylhydroxymethyl]-2,6,6-trimethylcyclohexanone (2′b)** (251 mg, 67% isolated yield): mp 83–84 °C; IR 3600–3410, 3120, 1679, and 1600 cm^{-1}; ^1H NMR δ 1.07 (3 H, s, CH_3-2), 1.17 (3 H, s, CH_3-6), 1.18 (3 H, s, CH_3-6), 3.17 (1 H, d, J = 6.5 Hz, OH), 4.76 (1 H, d, J = 6.5 Hz, CH-Fur), 6.30 (1 H, m, H-β′), 7.31 (1 H, m, H-α), and 7.34 (1 H, m, H-α′); ^{13}C NMR δ 17.22, 24.06, 27.08, 27.89, 31.58, 38.51, 44.70, 52.04, 72.81, 110.03, 125.14, 140.35, 142.44, and 222.89; MS m/z (relative intensity) 236 (3, M^+), 140 (85), 125 (100), 97 (64), 95 (22), 84 (43), 69 (31), and 55 (33). Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 71.20; H, 8.46.

B. Via the Magnesium Enolate. The 2-bromo-2,6,6-trimetylcyclohexanone (869 mg, 3.97 mmol)[33] was treated as in a previous procedure to obtain only an aldol product identified as **(2*RS*)-2-[(*SR*)-3-furylhydroxymethyl]-2,6,6-trimethylcyclohexanone (2′a)** (487 mg, 52% isolated yield): mp 60–61 °C; IR 3570–3300, 3130, 1681, and 1590 cm^{-1}; ^1H NMR δ 1.09 (3 H, s, CH_3-2), 1.18 (3 H, s, CH_3-6), 1.24 (3 H, s, CH_3-6), 4.29 (1 H, d, J = 2.1 Hz, OH), 4.83 (1 H, d, J = 2.1 Hz, CH-Fur), 6.34 (1 H, m, H-β′), and 7.34 (2 H, m, H-α and H-α′); ^{13}C NMR δ 17.11, 19.42, 27.09, 27.62, 33.84, 38.83, 44.72, 51.07, 72.21, 110.16, 124.53, 140.47, 141.96, and 205.05; MS m/z (relative intensity) 236 (5, M^+), 140 (72), 125 (100), 97 (32), 84 (11), 69 (20), and 55 (22). Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 71.20; H, 8.60.

C. Via the Lithium Enolate. The 2,2,6-trimethylcyclohexanone (700 mg, 5.00 mmol) was treated as in a previous procedure to obtain a mixture (472 mg, 40% isolated yield; the reaction time was 5 s) of the two different aldol products **2′b:2′a** in 26:74 ratio.

(2*RS*,6*RS*)-2-[3-Furyloxomethyl]-2,6-dimethylcyclohexanone (3a) and (2*RS*,6*SR*)-2-[3-Furyloxomethyl]-2,6-dimethylcyclohexanone (3b). Jones reagent (0.5 mL) was added dropwise with stirring to a solution of the corresponding aldol product (44 mg, 0.2 mmol) in acetone (3.0 mL) at 0 °C. The resulting mixture was stirred at 0 °C for an additional 15 min. 2-Propanol was added in small portions to discharge a brown color in the upper layer. The mixture was concentrated in vacuo to afford a crude product, which was dissolved with water and extracted with ether. The organic layers were washed with water and brine, dried (Na_2SO_4), and filtered. The solvent was evaporated and the crude product was purified by flash chromatography using hexane–ether (4:1) as the eluent.

Aldols **2a** and **2b** afforded the same oily 1,3-diketone **3a**, (41 mg, 96% yield) and (42 mg, 97% yield), respectively: IR 1700 and 1650 cm^{-1}; ^1H NMR δ 1.20 (3 H, d, J = 8 Hz, CH_3-6), 1.46 (3 H, s, CH_3-2), 2.50 (1 H, m, H-6), 6.59 (1 H, m, H-β′), 7.38 (1 H, m, H-α′), and 7.85 (1 H, m, H-α).

Aldols **2c** and **2d** afforded the same oily 1,3-diketone **3b**, (41 mg, 96% yield) and (43 mg, 98% yield), respectively: IR 1690 and 1650 cm^{-1}; ^1H NMR δ 0.98 (3 H, d, J = 8 Hz, CH_3-6), 1.36 (3 H, s, CH_3-2), 2.30 (1 H, m, H-6), 6.72 (1 H, m, H-β′), 7.38 (1 H, m, H-α′), and 7.87 (1H, m, H-α).

Acetylation of the Aldol Products 2a–d and 2′a,b. General Procedure. The corresponding aldol product (0.5 mmol) was treated with acetic anhydride (0.6 mL) and pyridine (0.6 mL) at rt for 4 h. The reaction mixture was poured onto ice, and the heterogeneous mixture was stirred and gradually warmed to rt (1 h). It was then extracted three times with ether. The combined extracts were washed with aqueous HCl (2 N), $NaHCO_3$ (5%), and brine and then dried (Na_2SO_4). The solvent was evaporated and the crude product was purified by flash chromatography using hexane–ether (2:1) as the eluent.

From the Aldol Products 2a–d. The keto acetate from the aldol **2a** (125 mg, 95% yield) was an oily product: IR 1725 and 1700 cm^{-1}; ^1H NMR δ 0.99 (3 H, d, J = 6.5 Hz, CH_3-6), 1.31 (3 H, s, CH_3-2), 2.06 (3 H, s, CH_3CO), 2.64 (1 H, m, H-6), 6.19 (1 H, s, CHOCO), 6.32 (1 H, m, H-β′), 7.31 (1 H, m, H-α), and 7.32 (1 H, m, α′).

The keto acetate from the aldol **2b** (125 mg, 95% yield) was an oily product: IR 1735 and 1710 cm^{-1}; ^1H NMR δ 1.01 (3 H, d, J = 7.1 Hz, CH_3-6), 1.07 (3 H, s, CH_3-2), 1.99 (3 H, s, CH_3CO), 2.56 (1 H, m, H-6), 6.17 (1 H, s, CHOCO), 6.33 (1 H, m, H-β′), 7.33 (1 H, m, H-α), and 7.36 (1 H, m, H-α′).

The keto acetate from the aldol **2c** (128 mg, 97% yield) was an oily product: IR 1730 and 1700 cm^{-1}; ^1H NMR δ 1.01 (3 H, d, J = 6.4 Hz, CH_3-6), 1.08 (3 H, s, CH_3-2), 2.12 (3 H, s, CH_3CO), 2.72 (1 H, m, H-6), 6.17 (1 H, m, H-β′), 6.49 (1 H, s, CHOCO), 7.31 (1 H, m, H-α), and 7.31 (1 H, m, H-α′).

The keto acetate from the aldol **2d** (129 mg, 98% yield) was a crystalline product: mp 64–65 °C; IR 1725 and 1695 cm^{-1}; ^1H NMR δ 1.00 (3 H, d, J = 6.4 Hz, CH_3-6), 1.05 (3 H, s, CH_3-2), 1.98 (3 H, s, CH_3CO), 2.82 (1 H, m, H-6), 6.38 (1 H, m, H-β′), 6.48 (1 H, s, CHOCO), 7.39 (1 H, m, H-α), and 7.43 (1 H, m, H-α′).

From the Aldol Products 2′a,b. The keto acetate from the aldol **2′a** (133 mg, 96% yield) was a crystalline product: mp 68–69 °C; IR 1750 and 1690 cm^{-1}; ^1H NMR δ 0.95 (3 H, s, CH_3-6), 1.12 (3 H, s, CH_3-6), 1.20 (3 H, s, CH_3-2), 2.07 (3 H, s, CH_3-CO), 6.22 (1 H, s, H-β′), 6.29 (1 H, s, CHOCO), 7.21 (1 H, m, H-α) and 7.29 (1 H, m, H-α′).

The keto acetate from the aldol **2′b** (138 mg, 99% yield) was a crystalline product: mp 65–67 °C; IR 1750 and 1690 cm^{-1}; ^1H NMR δ 1.03 (3 H, s, CH_3-6), 1.09 (3 H, s, CH_3-2), 1.16 (3 H, s, CH_3-6), 1.95 (3 H, s, CH_3CO), 6.15 (1 H, s, CH-OCO), 6.33 (1 H, m, H-β′), 7.34 (1 H, m, H-α), and 7.36 (1 H, m, H-α′).

1-(3-Furyl)-4a-hydroxyoctahydro-2-benzopyran-3-ones 4a–d and 4′a,b. General Procedure. A solution of the corresponding keto acetate (2.4 mmol) in dry ether (5 mL) was added dropwise at −78 °C with stirring under N_2 to a solution of lithium diisopropylamide (3.1 mmol) in the same solvent (5 mL), prepared as shown in preceding reactions. The mixture was stirred at −78 °C for an additional 30 min, and then saturated aqueous NH_4Cl (10 mL) was added and the resulting heterogeneous mixture was stirred and gradually warmed to rt. After the usual workup the solvent was evaporated and the residue was purified by flash chromatography using hexane–ether (2:3) as the eluent.

A. From 2,6-Dimethylcyclohexanone. The keto acetate from **2a** afforded **(1*RS*,4a*RS*,5*SR*,8a*SR*)-1-(3-furyl)-4a-hydroxy-5,8a-dimethyloctahydro-2-benzopyran-3-one (4a)** (570 mg, 90% yield): mp 133–135 °C; IR 3300–3050 and 1725 cm^{-1}; ^1H NMR δ 0.90 (3 H, d, J = 7.2 Hz, CH_3-5), 0.99 (3 H, s, CH_3-8a), 2.56 (1 H, d, J = 17.0 Hz, H-4), 2.70 (1 H, d, J = 17.0 Hz, H-4), 5.77 (1 H, s, H-1), 6.38 (1 H, m, H-β′), 7.38 (1 H, m, H-α), and 7.39 (1 H, m, H-α′); ^{13}C NMR δ 14.21, 14.80, 19.99, 29.14, 34.37, 39.60, 39.80 (2), 73.13, 79.94, 110.18, 121.24, 140.82, 142.58, and 170.87; MS m/z (relative intensity) 264 (12, M^+), 246 (73), 231 (8), 168 (11), 153 (12), 126 (100), 111 (42), 108 (40), 93 (30), 84 (20), 69 (14), and 55 (20). Anal. Calcd for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63. Found: C, 68.10; H, 7.58.

The keto acetate from **2b** afforded **(1*RS*,4a*SR*,5*RS*,8a*RS*)-1-(3-furyl)-4a-hydroxy-5,8a-dimethyloctahydro-2-benzopyran-3-one (4b)** (577 mg, 91% yield): mp 128–131 °C; IR 3300–3050 and 1725 cm^{-1}; ^1H NMR δ 0.93 (3 H, d, J = 6.4 Hz, CH_3-5), 0.94 (3 H, s, CH_3-8a), 2.50 (1 H, d, J = 19.0 Hz, H-4), 2.85 (1 H, d, J = 19.0 Hz, H-4), 5.66 (1 H, s, H-1), 6.38 (1 H, m, β′), 7.38 (1 H, m, α), and 7.39 (1 H, m, α′); ^{13}C NMR δ 13.99, 15.90, 19.70, 27.44, 31.90, 34.90, 36.88, 40.84, 74.40, 78.50, 110.30, 121.12, 140.99, 142.50, and 171.25; MS m/z (relative intensity) 264 (25, M^+), 246 (9), 222 (32), 168 (9), 127 (59), 126 (100), 111 (82), 94 (29), 84 (41), 69 (20), and 55 (28). Anal. Calcd for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63. Found: C, 68.19; H, 7.59.

The keto acetate from **2c** afforded **(1*RS*,4a*SR*,5*SR*,8a*RS*)-1-(3-furyl)-4a-hydroxy-5,8a-dimethyloctahydro-2-benzopyran-3-one (4c)** (570 mg, 90% yield):

(33) The 2-bromo-2,6,6-trimethylcyclohexanone was prepared as reported by: Djerassi, C.; Scholz, C. R. *J. Am. Chem. Soc.* **1948**, *70*, 417. To complete the reaction 1 h was required and a quantitative yield was obtained.

mp 127–129 °C; IR 3300–3050 and 1725 cm^{-1}; ^1H NMR δ 0.99 (3 H, s, CH_3-8a), 1.13 (3 H, d, J = 8.0 Hz, CH_3-5), 2.57 (1 H, d, J = 18.0 Hz, H-4), 3.08 (1 H, d, J = 18.0 Hz, H-4), 5.52 (1 H, s, H-1), 6.38 (1 H, m, β'), 7.38 (1 H, m, α), and 7.39 (1 H, m, α'); ^{13}C NMR δ 15.25, 16.02, 17.62, 27.50, 28.76, 39.29, 41.06, 42.46, 79.01, 73.58, 110.46, 120.77, 141.30, 142.60 and 171.54. Anal. Calcd for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63. Found: C, 68.20; H, 7.71.

The keto acetate from **2d** afforded **(1*RS*,4a*RS*,5*RS*,8a*SR*)-1-(3-furyl)-4a-hydroxy-5,8a-dimethyloctahydro-2-benzopyran-3-one (4d)** (617 mg, 93% yield): mp 131–133 °C; IR 3300–3050 and 1725 cm^{-1}; ^1H NMR δ 0.95 (3 H, s, CH_3-8a), 1.00 (3 H, d, J = 6.5 Hz, CH_3-5), 2.65 (1 H, d, J = 18.0 Hz, H-4), 3.00 (1 H, d, J = 18.0 Hz, H-4), 5.77 (1 H, s, H-1), 6.39 (1 H, m, β'), 7.40 (1 H, m, α), and 7.42 (1 H, m, α'); ^{13}C NMR δ 15.07, 16.00, 20.30, 29.69, 29.70, 34.50, 38.74, 40.67, 72.42, 77.23, 104.80, 121.00, 140.50, 142.80, and 171.50; MS m/z (relative intensity) 264 (6, M^+), 191 (6), 136 (7), 126 (100), 111 (19), 95 (13), 81 (12), 69 (18), and 55 (20). Anal. Calcd for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63. Found: C, 68.20; H, 7.69.

B. From 2,2,6-Trimethylcyclohexanone. The keto acetate from **2'a** afforded **(1*RS*,8a*SR*)-1-(3-furyl)-4a-hydroxy-5,5,8a-trimethyloctahydro-2-benzopyran-3-one (4'a)** (634 mg, 95% yield): mp 130–132 °C; IR 3420–3350 and 1710 cm^{-1}; ^1H NMR δ 0.98 (3 H, s), 1.04 (3 H, s), 1.11 (3 H, s), 2.60 (1 H, d, J = 18.9 Hz, H-4), 2.98 (1 H, d, J = 18.2 Hz, H-4), 5.70 (1 H, s, CHOCO), 6.39 (1 H, m, β'), 7.39 (1 H, m, H-α), and 7.40 (1 H, m, H-α'); ^{13}C NMR δ 17.46, 18.26, 25.07, 27.15, 31.06, 35.82, 37.59, 38.71, 41.08, 74.77, 79.40, 110.10, 121.87, 140.51, 142.61, and 170.69; MS m/z (relative intensity) 278 (22, M^+), 236 (20), 182 (18), 167 (34), 140 (100), 125 (85), 107 (25), 95 (30), 84 (27), 69 (26), and 55 (24). Anal. Calcd for $C_{16}H_{22}O_4$: C, 69.04; H, 7.97. Found: C, 69.08; H, 7.92.

The keto acetate from **2'b** afforded **(1*RS*,8a*RS*)-1-(3-furyl)-4a-hydroxy-5,5,8a-trimethyloctahydro-2-benzopyran-3-one (4'b)** (647 mg, 97% yield): mp 159–161 °C; IR 3440–3350 and 1715 cm^{-1}; ^1H NMR δ 0.96 (3 H, s), 1.03 (3 H, s), 1.15 (3 H, s), 2.60 (1 H, d, J = 18.9 Hz, H-4), 3.06 (1 H, d, J = 18.9 Hz, H-4), 5.55 (1 H, s, CHOCO), 6.37 (1 H, m, β'), 7.38 (2 H, m, H-α and H-α'); ^{13}C NMR δ 17.34, 17.77, 23.93, 26.92, 27.56, 37.44, 38.82, 39.57, 41.59, 75.54, 78.56, 110.72, 121.36, 141.69, 142.56, and 171.61; MS m/z (relative intensity) 278 (5, M^+), 236 (7), 140 (100), 125 (44), 107 (6), 95 (13), 84 (15), 69 (17), and 55 (18). Anal. Calcd for $C_{16}H_{22}O_4$: C, 69.04; H, 7.97. Found: C, 69.09; H, 8.03.

1-(3-Furyl)hexahydro-2-benzopyran-3-ones 5a–d and 5'a,b. General Procedure. $SOCl_2$ (0.9 mL, 12.0 mmol) was added at 0 °C with stirring under N_2 to a solution of the corresponding hydroxy lactone (6.0 mmol) in dry CH_2Cl_2 (30 mL) and dry pyridine (2.0 mL, 24.7 mmol). The mixture was stirred at 0 °C for 5 min and then poured onto ice. The heterogeneous mixture was gradually warmed to rt; it was then extracted three times with CH_2Cl_2. The combined extracts were washed with aqueous HCl (2 N), $NaHCO_3$ (5%), and brine and then dried (Na_2SO_4). The solvent was evaporated, and in all cases dehydrated products were obtained in quantitative yield.

A. From 2,6-Dimethylcyclohexanone. The hydroxy lactone **4a** afforded a mixture (1:1) of two compounds which were separated by flash chromatography using hexane–ether (3:2) as the eluent.

The first one eluted was identified as **(1*RS*,5*SR*,8a*RS*)-1-(3-furyl)-5,8a-dimethyl-1,5,6,7,8,8a-hexahydro-3*H*-2-benzopyran-3-one (5a)**: mp 154–156 °C; IR 1710 cm^{-1}; ^1H NMR δ 1.07 (3 H, s, CH_3-8a), 1.17 (3 H, d, J = 6.5 Hz, CH_3-5), 2.40 (1 H, m, H-5), 5.05 (1 H, s, H-1), 5.85 (1 H, s, H-4), 6.44 (1 H, m, H-β'), 7.48 (1 H, m, H-α), and 7.47 (1 H, m, H-α'); ^{13}C NMR δ 17.66 (2), 20.81, 34.55, 35.67 (2), 39.28, 81.50, 110.09, 112.39, 120.09, 141.04, 142.12, 165.25, and 171.07; MS m/z (relative intensity) 246 (1, M^+), 150 (100), 135 (38), 122 (8), 108 (15), 91 (13), 79 (16), 65 (6), 55 (7), and 53 (10). Anal. Calcd for $C_{15}H_{18}O_3$: C, 73.15; H, 7.37. Found: C, 73.18; H, 7.43.

The second compound was identified as **(1*RS*,8a*RS*)-1-(3-furyl)-5,8a-dimethyl-3,4,6,7,8,8a-hexahydro-1*H*-2-benzopyran-3-one (5d)**: mp 76–77 °C; IR 1750 cm^{-1}; ^1H NMR δ 1.00 (3 H, s, CH_3-8a), 1.59 (3 H, s, CH_3-5), 2.00 (2 H, m, H-6), 3.38 (2 H, m, H-4), 5.00 (1 H, s, H-1), 6.40 (1 H, m, H-β'), 7.39 (1 H, m, H-α), and 7.44 (1 H, m, H-α'); ^{13}C NMR δ 16.93, 17.45, 18.32, 30.90, 32.16, 32.17, 37.50, 81.61, 109.63, 120.54, 125.45, 127.96, 140.50, 142.37, and 170.58; MS m/z (relative intensity) 246 (27, M^+), 150 (5), 122 (100), 107 (86), 93 (44), 79 (19), 67 (5), and 55 (7). Anal. Calcd for $C_{15}H_{18}O_3$: C, 73.15; H, 7.37. Found: C, 73.11; H, 7.41.

The hydroxy lactone **4b** afforded **(1*RS*,5*RS*,8a*SR*)-1-(3-furyl)-5,8a-dimethyl-1,5,6,7,8,8a-hexahydro-3*H*-2-benzopyran-3-one (5b)**: mp 84–87 °C; IR 1700 cm^{-1}; ^1H NMR δ 1.15 (3 H, d, J = 6.4 Hz, CH_3-5), 1.33 (3 H, s, CH_3-8a), 2.53 (1 H, m, H-5), 5.07 (1 H, s, H-1), 5.86 (1 H, s, H-4), 6.35 (1 H, m, H-β'), 7.36 (1 H, m, H-α), and 7.40 (1 H, m, H-α'); ^{13}C NMR δ 17.35, 20.92, 23.57, 33.82 (2), 36.34, 39.92, 80.81, 109.98, 111.79, 121.76, 141.56, 143.09, 164.51, and 170.28; MS m/a (relative intensity) 246 (4, M^+), 202 (2), 150 (100), 135 (36), 122 (9), 108 (14), 91 (11), 79 (14), 65 (5), 55 (7), and 53 (7). Anal. Calcd for $C_{15}H_{18}O_3$: C, 73.15; H, 7.37. Found: C, 73.20; H, 7.40.

The hydroxy lactone **4c** afforded **(1*RS*,5*SR*,8a*SR*)-1-(3-furyl)-5,8a-dimethyl-1,5,6,7,8,8a-hexahydro-3*H*-2-benzopyran-3-one (5c)**: mp 65–68 °C; IR 1715 cm^{-1}; ^1H NMR δ 1.26 (3 H, d, J = 7.4 Hz, CH_3-5), 1.49 (3 H, s, CH_3-8a), 2.72 (1 H, m, H-5), 4.99 (1 H, s, H-1), 5.86 (1 H, s, H-4), 6.28 (1 H, m, β'), 7.33 (1 H, m, α), and 7.37 (1 H, m, α'); ^{13}C NMR δ 16.13, 22.37, 27.33, 29.57, 32.25, 34.60, 38.28, 82.30, 109.70, 115.24, 122.21, 141.71, 143.09, 163.70, and 168.84. Anal. Calcd for $C_{15}H_{18}O_3$: C, 73.15; H, 7.37. Found: C, 73.22; H, 7.33.

The hydroxy lactone **4d** afforded a compound which was identified as **5d**.

B. From 2,2,6-Trimethylcyclohexanone. The hydroxy lactone **4'a** afforded **(1*RS*,8a*RS*)-1-(3-furyl)-5,5,8a-trimethyl-1,5,6,7,8,8a-hexahydro-3*H*-2-benzopyran-3-one (5'a)**: mp 138–139 °C; IR 1710 cm^{-1}; ^1H NMR δ 1.14 (3 H, s, CH_3-8a), 1.21 (3 H, s, CH_3-5), 1.53 (3 H, s, CH_3-8a), 5.01 (1 H, s, H-1), 5.98 (1 H, s, H-4), 6.40 (1 H, m, H-β'), 7.39 (1 H, m, H-α), and 7.46 (1 H, m, H-α'); ^{13}C NMR δ 16.87, 18.64, 30.04, 30.15, 34.45, 35.87, 38.70, 38.99, 81.99, 109.93, 113.24, 119.85, 140.98, 142.43, 165.48, and 175.01; MS m/z (relative intensity) 260 (13, M^+), 164 (100), 149 (41), 136 (10), 122 (89), 107 (35), 93 (23), 79 (16), 67 (9), and 55 (12). Anal. Calcd for $C_{16}H_{20}O_3$: C, 73.82; H, 7.74. Found: C, 73.89; H, 7.67.

The hydroxy lactone **4'b** afforded **(1*RS*,8a*SR*)-1-(3-furyl)-5,5,8a-trimethyl-1,5,6,7,8,8a-hexahydro-3*H*-2-benzopyran-3-one (5'b)**: mp 95–97 °C; IR 1700 cm^{-1}; ^1H NMR δ 1.22 (3 H, s, CH_3-5), 1.24 (3 H, s, CH_3-5), 1.53 (3 H, s, CH_3-8a), 4.96 (1 H, s, H-1), 6.02 (1 H, s, H-4), 6.27 (1 H, m, H-β'), 7.32 (1 H, m, H-α), and 7.35 (1 H, m, H-α'); ^{13}C NMR δ 17.17, 28.14, 30.03, 30.97, 33.23, 35.84, 38.63, 65.57, 82.55, 109.75, 114.54, 122.40, 141.87, 143.08, 164.18 and 171.55; MS m/z (relative intensity) 260 (2, M^+), 164 (100), 149 (85), 108 (30), 93 (19), 77 (19), 67 (9), and 55 (15). Anal. Calcd for $C_{16}H_{20}O_3$: C, 73.82; H, 7.74. Found: C, 73.90; H, 7.80.

(1*RS*,4*SR*,8a*RS*)-1-(3-Furyl)-5,8a-dimethyl-4-iodo-3,4,6,7,8,8a-hexahydro-1*H*-2-benzopyran-3-one (6). A solution of the unsaturated lactone **5d** (180 mg, 0.73 mmol) in dry THF (2.5 mL) was added dropwise at −78 °C with stirring under N_2 to a solution of lithium diisopropylamide (0.85 mmol) in the same solvent (1.5 mL), prepared as shown in preceding reactions. The mixture was stirred at −78 °C for an additional 45 min and then a solution of I_2 (412 mg, 1.62 mmol) in dry THF (2 mL) was added dropwise over a period of 10 min at −78 °C. The brown I_2 color disappeared immediately on addition of the first drops and a light yellow precipitate formed; afterwards the color remained dark brown.

This heterogeneous mixture was stirred under these conditions for an additional 1 h, and then saturated aqueous NH_4Cl (10 mL) was added and the resulting mixture was stirred and gradually warmed to rt. After the usual workup the crude material (206 mg) was chromatographed on silica gel to obtain three different compounds:

4-Iodo lactone **6** was a crystalline product (34 mg, 13% yield) eluted with a mixture of hexane–ether (7:3): mp 150–152 °C; IR 1740 cm^{-1}; ^1H NMR δ 0.97 (3 H, s, CH_3-8a), 1.86 (3 H, s CH_3-5), 2.05 (2 H, m, H-6), 4.24 (1 H, s, H-4), 5.22 (1 H, s, H-1), 6.35 (1 H, m, H-β'), 7.33 (1 H, m, H-α), and 7.34 (1 H, m, H-α'); ^{13}C NMR δ 17.22, 19.99, 21.27, 31.32, 31.42, 38.37, 45.93, 79.95, 100.26, 120.61, 127.19, 132.90, 141.22, 142.56, and 170.84; MS m/z (relative intensity) 372 (2, M^+), 246 (78), 231 (21), 201 (28), 148 (100), 133 (27), 122 (80), 107 (51), 105 (46), 91 (35), 77 (26), 69 (15), and 55 (21). Anal. Calcd for $C_{15}H_{17}O_3I$: C, 48.41; H, 4.60. Found: C, 48.33; H, 4.65.

(1*RS*,5*RS*,8a*RS*)-1-(3-Furyl)-5,8a-dimethyl-5-hydroxy-1,5,6,7,8,8a-hexahydro-3*H*-2-benzopyran-3-one (7a) was a crystalline product (73 mg, 38% yield) eluted with a mixture of hexane–ether (1:4): mp 163–170 °C; IR 3360 and 1710 cm^{-1}; ^1H NMR δ 1.28 (3 H, s, CH_3-8a), 1.50 (3 H, s, CH_3-5), 2.00 (2 H, m, H-6), 5.04 (1 H, S, H-1), 6.13 (1 H, s, H-4), 6.43 (1 H, m, H-β'), 7.42 (1 H, m, H-α), and 7.47 (1 H, m, H-α'); ^{13}C NMR δ 17.22, 19.19, 28.26, 36.01, 39.41, 40.27, 70.36, 83.63, 111.21, 114.55, 121.55, 142.81, 144.22, 168.14, and 170.92; MS m/z (relative intensity) 262 (8, M^+), 166 (100), 151 (65), 138 (70), 121 (86), 105 (49), 95 (38), 79 (30), 67 (25), and 55 (27). Anal. Calcd for $C_{15}H_{18}O_4$: C, 68.69; H, 6.92. Found: C, 68.60; H, 6.85.

(1*RS*,5*SR*,8a*RS*)-1-(3-Furyl)-5,8a-dimethyl-5-hydroxy-1,5,6,7,8,8a-hexahydro-3*H*-2-benzopyran-3-one (7b) was a crystalline product (20 mg, 10% yield) eluted with ether: mp 153–156 °C; IR 3440–3280 and 1720 cm^{-1}; ^1H NMR δ 1.12 (3 H, s, CH_3-8a), 1.47 (3 H, s, CH_3-5), 2.01 (2 H, m, H-6), 5.06 (1 H, s, H-1), 6.41 (1 H, s, H-4), 6.42 (1 H, m, H-β'), 7.41 (1 H, m, H-α), and 7.48 (1 H, m, H-α'); ^{13}C NMR δ 18.32, 18.55, 30.44, 34.68, 39.62, 41.04, 71.75, 82.36, 110.09, 113.69, 120.09, 141.28, 142.87, 165.59, and 172.60; MS m/z (relative intensity) 262 (4, M^+), 166 (100), 151 (64), 138 (70), 121 (88), 105 (47), 95 (37), 79 (31), 67 (21), and 55 (19s). Anal. Calcd for $C_{15}H_{18}O_4$: C, 68.69; H, 6.92. Found: C. 68.78; H, 7.00.

(1*RS*,4*SR*,8a*RS*)-1-(3-Furyl)-5,8a-dimethyl-4-(benzylseleno)-3,4,6,7,8,8a-hexahydro-1*H*-2-benzopyran-3-one (8a) and (1*RS*,5*RS*,8a*RS*)-1-(3-furyl)-5,8a-dimethyl-5-(benzylseleno)-1,5,6,7,8,8a-hexahydro-3*H*-2-benzopyran-3-one (8b). A solution of benzeneselenenyl chloride (159 mg, 0.83 mmol) in dry tetrahydrofuran (1 mL) was added at −78 °C under N_2 to a solution of the lithium dienolate from the unsaturated lactone **5d** (from 200 mg, 0.81 mmol) in the same solvent (3 mL), prepared as shown in preceding reactions.

The reaction was quenched after 3 h with saturated aqueous NH_4Cl (15 mL). The products were isolated by extraction with ether. Standard workup left a residue (310 mg) which was chromatographed on silica gel.

The first compound **8a** (166 mg, 51% yield), hexane–ether (2:1) as eluent, was a crystalline product: mp 192–198 °C; IR 1720 cm^{-1}; ^1H NMR δ 0.97 (3 H, s, CH_3-8a), 1.87 (3 H, s, CH_3-5), 4.74 (1 H, s, H-4), 5.55 (1 H, s, H-1), 6.44 (1 H, m, H-β'), and 7.32–7.69 (7 H, m): ^{13}C NMR δ 17.14, 18.38, 20.10, 30.91, 31.60, 38.36, 41.48, 79.87, 110.09, 120.51, 127.45, 128.28, 129.15, 131.46, 134.90, 135.99, 141.00, 142.61, and 169.20. Anal. Calcd for $C_{21}H_{22}O_3Se$: C, 62.84; H, 5.52. Found: C, 62.90; H, 5.45.

The second **8b** (130 mg, 40% yield), hexane–ether (2:1) as eluent, was a crystalline product: mp 153–155 °C; IR 1720 cm^{-1}; ^1H NMR δ 1.54 (3 H, s, CH_3-8a), 1.60 (3 H, s, CH_3-5), 4.99 (1 H, s, H-1), 5.24 (1 H, s, H-4), 6.44 (1 H, m, H-β'), and 7.31–7.51 (7 H, m); ^{13}C NMR δ 18.27, 21.17, 29.98, 35.05, 38.90, 39.56, 65.73, 82.25, 110.21, 114.51, 120.12, 127.65, 128.98, 129.72, 138.34, 141.33, 142.73, 166.92, and 180.95; MS m/z (relative intensity) 401 (10, M^+), 245 (100), 217 (33), 149 (42), 95 (44), and 77 (31). Anal. Calcd for $C_{21}H_{22}O_3Se$: C, 62.84; H, 5.52. Found: C, 62.76; H, 5.43.

(1*RS*,8a*RS*)-1-(3-Furyl)-5,8a-dimethyl-5-hydroperoxy-1,5,6,7,8,8a-hexahydro-3*H*-2-benzopyran-3-one (9a/b). A solution of *tert*-butyl hydroperoxide (0.05 mL, 0.41 mmol) in *tert*-butyl peroxide (80%) was added to a heterogeneous mixture of selenium dioxide (11 mg, 0.10 mmol) in dry CH_2Cl_2 (0.50 mL). The mixture was stirred at rt over a period of 30 min; after this time the mixture became a homogeneous solution.

Over the former, a solution of the unsaturated lactone **5d** (100 mg, 0.41 mmol) in dry CH_2Cl_2 (0.5 mL) was added rapidly. After 42 h ether (10 mL) was added and the solution was washed with aqueous $NaHSO_3$ (10%), water, and brine and then dried (Na_2SO_4). Evaporation of the solvent left a crude product mixture (107 mg) which was flash chromatographed on silica gel.

The first fraction eluted (70 mg, 61% yield), hexane–ether (1:1) as the eluent, was a mixture of compounds **9ab** which proved positive in the peroxide test (KI, aqueous acetic acid). From the ^1H NMR spectra of the mixture, for **9a** 1.21 (3 H, s, CH_3-8a), 1.48 (3 H, s, CH_3-5), 5.07 (1 H, s, H-1), 6.16 (1 H, s, H-4), 6.41 (1 H, m, H-β'), 7.40 (1 H, m, H-α), and 7.46 (1 H, m, H-α') and for **9b** 1.10 (3 H, s, CH_3-8a), 1.47 (3 H, s, CH_3-5), 5.06 (1 H, s, H-1), 6.41 (1 H, s, H-4), 6.42 (1 H, m, H-β'), 7.41 (1 H, m, H-α), and 7.48 (1 H, m, H-α'). This mixture was reduced, without isolating the two hydroperoxides, by adding a solution of them in dry methanol (1 mL) to a cooled (0 °C) solution of $NaBH_4$ (4 mg, 0.38 mequiv) in the same solvent (1 mL) and then stirring until the peroxide test (KI, aqueous acetic acid) became negative. The resulting alcohols were isolated by dilution with water, extraction with ether, washing with water, drying (Na_2SO_4), concentration, and evaporation of the solvent. The two alcohols were separated by flash chromatography to obtain (63 mg, 95% yield) 1.0:1.4 ratio for **7a**:**7b**.

The second one eluted (10 mg, 9% yield), hexane–ether (1:4) as the eluent, was a crystalline compound identified as the hydroxylated product **7a**.

The third compound (14 mg, 13% yield), ether as the eluent, was a crystalline product identified as the hydroxylated product **7b**.

(±)-Pyroangolensolide. A. From the 4-Iodo Lactone 6. A mixture of the 4-iodo lactone **6** (35 mg, 0.09 mmol) and lithium chloride (5 mg, 0.10 mmol) was dissolved in dry dimethylformamide (1 mL) and the mixture was refluxed, under N_2, for 1 h. The mixture was allowed to cool, then saturated brine was added to it and the product extracted with ether. The organic layer was washed successively with aqueous HCl (2 N), aqueous $NaHCO_3$ (5%), and brine, and then dried (Na_2CO_4), and evaporated. The residue was purified by chromatography, using hexane–ether (3:2) as the eluent, to give (±)-pyroangolensolide (20 mg, 87% yield): ^{13}C NMR δ 15.84, 18.73, 22.02, 29.88, 37.15, 80.62, 109.93 (2), 120.15, 129.15, 136.03, 140.99, 142.69, 159.77, and 165.74; MS m/z (relative intensity) 244 (4, M^+), 184 (1), 148 (100), 133 (29), 119 (9), 91 (14), 77 (13), 65 (6), and 51 (8); all other data agreed with those reported in the literature.[3]

B. From Selenide Compounds 8a and 8b. The corresponding selenide (82 mg, 0.2 mmol) was dissolved in THF (3.5 mL) and was treated at 0 °C with acetic acid (24 μL, 0.4 mmol) and hydrogen peroxide (0.1 mL, 30%, 1.0 mmol). After 30 min the reaction was quenched by careful addition of saturated aqueous $NaHCO_3$. The heterogeneous mixture was stirred and gradually warmed to rt. Products were isolated by extraction with ether, and after the usual workup the crude product was flash chromatographed on silica gel.

The allyl selenide **8a** treated with the above procedure afforded three different products. The first one eluted, hexane–ether (3:2) as the eluent, was identified as (±)-pyroangolensolide (7 mg, 15% yield). The second one, eluted with ether, was identified as the hydroxylated product **7a** (18 mg, 34% yield), and the third compound was the hydroxylated product **7b** (19 mg, 36% yield).

The allyl selenide **8b** afforded these same products, (±)-pyroangolensolide (17 mg, 34% yield), the hydroxylated product **7a** (8 mg, 16% yield), and the hydroxylated product **7b** (10 mg, 19% yield). Another hydroxylated product (8 mg, 16% yield) was also isolated with ether; it was identified as **(1*RS*,8a*RS*)-1-(3-furyl)-5,8a-dimethyl-4-hydroxy-3,4,6,7,8,8a-hexahydro-1*H*-2-benzopyran-3-one (7c)**: IR 3520–3300 and 1740 cm^{-1}; ^1H NMR δ 1.01 (3 H, s, CH_3-8a), 1.85 (3 H, s, CH_3-5), 3.30 (1 H, s_w, OH), 4.92 (1 H, s_w, H-4), 5.02 (1 H, s, H-1), 6.41 (1 H, m, H-β'), 7.42 (1 H, m, H-α), and 7.46 (1 H, m, H-α').

C. From Hydroxylated Products 7a and 7b. Dehydrations were carried out with $SOCl_2$ in CH_2Cl_2/pyridine as in a preceding experiment to obtain, from both hydroxylated products **7a** and **7b**, (±)-pyroangolensolide at a quantitative yield.[34]

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Registry No. 1 (M = TMS), 116262-48-7; 1′ (M = MgBr), 136587-36-5; (±)-**2a**, 136587-14-9; (±)-**2′a**, 136587-30-9; (±)-**2b**, 136657-24-4; (±)-**2′b**, 136587-31-0; (±)-**2c**, 136657-25-5; (±)-**2d**, 136657-26-6; (±)-**3a**, 136587-15-0; (±)-**3b**, 136587-16-1; (±)-**4a**,

(34) When dehydrations were carried out at −30 °C, mixtures of (±)-pyroangolensolide and 5-chloro lactones were obtained at a 1.6:1.0 ratio.

136587-17-2; (±)-4'a, 136587-32-1; (±)-4b, 136616-25-6; (±)-4c, 136587-18-3; (±)-4d, 136587-19-4; (±)-4'b, 136587-33-2; (±)-5a, 126754-17-4; (±)-5'a, 136587-34-3; (±)-5b, 126754-18-5; (±)-5'b, 136587-35-4; (±)-5c, 136587-20-7; (±)-5d, 136587-21-8; (±)-6, 136587-22-9; (±)-7a, 136587-23-0; (±)-7b, 136587-24-1; (±)-7c, 136587-25-2; (±)-8a, 136587-26-3; (±)-8b, 136587-27-4; (±)-9a, 136587-28-5; (±)-9b, 136587-29-6; 3-furaldehyde, 498-60-2; (±)-pyroangolensolide, 52730-12-8.

Studies on the Synthesis of Aryl Ethers Using Arene–Manganese Chemistry

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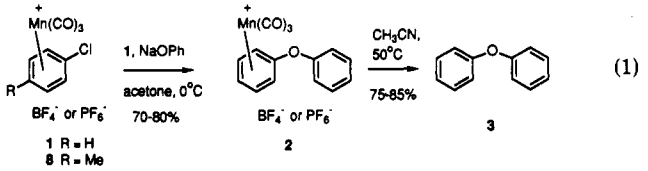
Selective arylation of polyfunctional phenols, using chlorobenzene- and *p*-chlorotoluene–manganese tricarbonyl cations, is described. The intermediate arene–manganese complexes are found to undergo stereo- and regioselective reactions with Schöllkopf's chiral glycine enolate equivalent to give dienyl–$Mn(CO)_3$ complexes. Treatment of these complexes with *N*-bromosuccinimide at room temperature, followed by hydrolysis of the dihydropyrazine, gives diaryl ethers in which one of the aromatic rings is an arylglycine methyl ester.

We are currently studying methods for the construction of diaryl ethers that have amino acid side chains attached to both aromatic rings,[1] which are expected to be useful for the preparation of synthetic building blocks for molecules related to the glycopeptide antibiotic vancomycin.[2] This paper reports observations on the chemistry of arene–manganese complexes that are showing promise in this general area of synthesis. It is known[3] that chloroarene–$Mn(CO)_3$ cations react with phenoxide nucleophiles to give, after decomplexation, diaryl ethers (eq 1). In this report



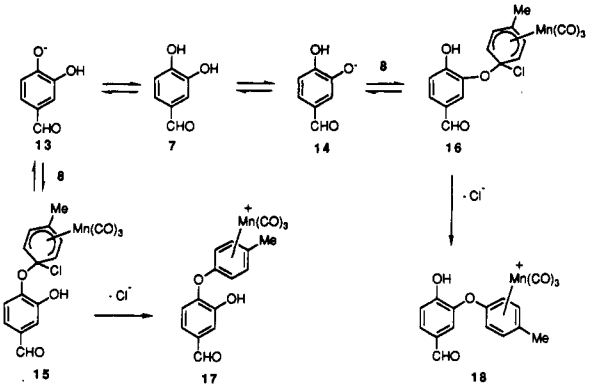
(1)

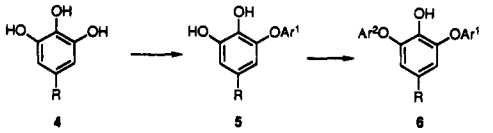
we address three questions:[4] (1) selectivity during the reaction of chloroarene–manganese complexes with some polyhydric phenols; (2) arylation of protected tyrosines and dipeptide derivatives; (3) the preparation of arylglycines derived from the *O*-aryltyrosines.

Results and Discussion

Selectivity during Arylation of Polyhydric Phenols. One of the requirements for preparation of subunits of the vancomycin family is that we should be able to arylate selectively phenolic compounds of general structure **4** to give unsymmetrical triaryl diethers **6**. We therefore examined selectivity during the reactions of gallic esters and 3,4-dihydroxybenzaldehyde derivatives with arene–$Mn(CO)_3$ cations.

Scheme I. Reversible Steps during the Reaction of 7 with 8 (Partial Mechanism)





Treatment of 3,4-dihydroxybenzaldehyde (**7**) with 1 equiv of sodium hydride, followed by reaction of the so-formed phenoxide with chlorotoluene–$Mn(CO)_3$ hexafluorophosphate (**8**) followed by in situ decomplexation, gave an approximately 95:5 mixture (by NMR) of the monoarylated compounds **9** and **10**. No diarylated product was observed. That the major product was **9** was confirmed by conversion to the methyl ether **11** and comparison of the NMR spectrum with authentic samples of **11** and the isomeric compound **12**, prepared by arylation of commercially available 4-hydroxy-3-methoxybenzaldehyde and 3-hydroxy-4-methoxybenzaldehyde, respectively.

The regioselectivity of arylation of **7** is somewhat surprising, based on the expectation that the more stable aryloxide **13** would be formed by deprotonation of the 4-hydroxy group. A plausible explanation is embodied in Scheme I, in which a series of reversible steps is envisioned

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(4) For earlier related studies from this laboratory, see: Pearson, A. J.; Bruhn, P. R.; Hsu, S. Y. *J. Org. Chem.* **1986**, *51*, 2137.

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